(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number
WO 01/28537 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/GB00/03944

(22) International Filing Date: 13 October 2000 (13.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9924522.7 15 October 1999 (15.10.1999) GB

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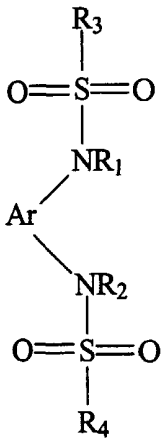
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ENZYME INHIBITORS



(I)

(57) Abstract: Bissulfonamide derivatives of formula (I) are capable of inhibiting: a) the biosynthesis of aromatic amino acids via the shikimate pathway and b) the catabolism of quinic acid, wherein: Ar is an aryl or heteroaryl group; R_1 and R_2 are the same or different and each represent hydrogen or alkyl or R_1 and R_2 together form a C_1-C_3 alkylene group, -CO- or -CS-; and R_3 and R_4 are the same or different and each represent -alkyl-aryl, -alkyl-heteroaryl, -alkenyl-aryl, -alkenyl-heteroaryl, -alkynyl-aryl-alkynyl-heterorayl, aryl or heteroaryl.

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ENZYME INHIBITORS

The present invention relates to a series of bissulfonamide derivatives which act as inhibitors of dehydroquinate synthetase and type II dehydroquinase enzymes.

Dehydroquinate synthetase and dehydroquinase enzymes form an essential part of the shikimate pathway by which erythrose-4-phosphate is converted to aromatic amino acids such as tryptophan, tyrosine and phenylalanine. Two types of biosynthetic dehydroquinase have been characterised, a Type I, or AroD, variety and a Type II, or AroQ, variety (Garbe *et al*, Mol. Gen. Genet., **228**, pgs 385-392 (1991), Hawkins *et al*, J. Gen. Microbiol. **139**, pgs 2891-2899 (1993)).

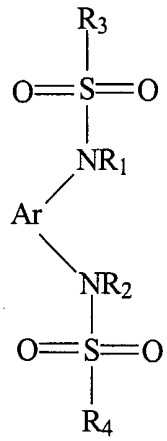
The shikimate pathway is essential in bacteria, algae, fungi and higher plants. Further, recent work shows evidence for the presence of enzymes of the shikimate pathway in apicomplexan parasites (Roberts *et al*, Nature, **393**, 1998, pgs 801-805). Compounds which can inhibit the biosynthesis of amino acids via the shikimate pathway therefore have a variety of commercial applications.

In addition to their biosynthetic function, type II dehydroquinase enzymes form an important part of the catabolic pathway by which quinic acid catabolism is effected. This catabolic pathway is found in many fungi and bacteria. Inhibitors of type II dehydroquinase enzymes therefore have commercial applications as fungicides and antibiotics.

Numerous diaminobissulfonamides are known. For example J. Chem. Soc., 1161 (1970) describes the synthesis of many of these compounds as intermediates to tetrahydrodibenzodiazocines, and J. Chem. Soc., 1170 (1962) describes electrophillic substitution reactions involving diaminobissulfonamides. No pharmaceutical utility is described in these publications, however. The synthesis and use of 1,2-bis(4-methylphenylsulfonylamino)-4,5-dibromobenzene as an intermediate to substituted phthalocyanines has been reported (Acta. Chemica. Scand., 658 (1995)). Some diaminobissulfonamides are of interest as candidates for non-linear optical studies (Acta. Cryst., 2395 (1995)).

Oncolytic activity has previously been ascribed to some diaminobissulfonamides (J. Med. Chem., 599 (1963)). The oncolytic activity was found to operate via inhibition of the biosynthetic conversion of 1,2-dimethyl-4,5-diaminobenzene to vitamin B_{12} by certain types of tumour cells (Biochem. Pharmacol., 1163 (1962)).

It has now surprisingly been found that particular bissulfonamide derivatives of the general formula (I) set out below act as inhibitors of dehydroquinate synthetase enzymes and as inhibitors of type II dehydroquinase enzymes. Accordingly, the present invention provides, in a first embodiment, the use of a bissulfonamide derivative of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inhibiting the biosynthesis of aromatic amino acids via the shikimate pathway,



(I)

wherein:

- Ar is an aryl or heteroaryl group;
- R_1 and R_2 are the same or different and each represent hydrogen or alkyl or R_1 and R_2 together form a C_1-C_3 alkylene group, -CO- or -CS-; and
- R_3 and R_4 are the same or different and each represent -alkyl-aryl, -alkyl-heteroaryl, -alkenyl-aryl, -alkenyl-heteroaryl, -alkynyl-aryl, -alkynyl-heteroaryl, aryl or heteroaryl.

Typically, the medicament is for use in the inhibition of a dehydroquinate synthetase enzyme, in particular AroB, and/or a type II dehydroquinase enzyme, in particular AroQ.

As used herein, an alkyl group or moiety is typically a linear or branched alkyl group or moiety containing from 1 to 6 carbon atoms, such as a C_1-C_4 alkyl group or moiety, for example methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl.

An alkyl group or moiety may be unsubstituted or substituted at any position. Typically, it is unsubstituted or carries one or two substituents. Suitable substituents include halogen, cyano, nitro, amino, hydroxy, oxo and -CO_2R, -SOR and -$S(O)_2$R wherein R is hydrogen or alkyl.

As used herein, an alkenyl group or moiety is typically a linear or branched alkenyl group or moiety containing from 2 to 6 carbon atoms, such as a C_2-C_4 alkenyl group or moiety, for example ethenyl, propenyl and butenyl.

An alkenyl group or moiety may be unsubstituted or substituted at any position. Typically, it is unsubstituted or carries one or two substituents. Suitable substituents include halogen, amino and hydroxy.

As used herein, an alkynyl group or moiety is typically a linear or branched alkynyl group or moiety containing from 2 to 6 carbon atoms, such as a C_2-C_4 alkynyl group or moiety, for example ethynyl, propynyl and butynyl.

An alkynyl group or moiety may be substituted or unsubstituted at any position. Typically, it is unsubstituted or carries one or two substituents. Suitable substituents include halogen, amino and hydroxy.

A C_1-C_3 alkylene group is a methylene, ethylene or propylene group. It may be unsubstituted or substituted at any position. Typically, it is unsubstituted or carries one substituent. Suitable substituents include halogen, cyano, nitro, oxo and -CO_2R, -SOR and -$S(O)_2$R wherein R is hydrogen or alkyl.

As used herein, an aryl group is typically a C_6-C_{10} aryl group such as phenyl or naphthyl. Phenyl is preferred. An aryl group may be unsubstituted or substituted at any position. Typically, it carries 1, 2, 3 or 4 substituents. Suitable substituents include aryl, carbocyclyl, heteroaryl and heterocyclic groups, nitro,

cyano, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy, hydroxy, -CO_2R and -$S(O)_2R$ wherein R is aryl, heteroaryl, hydrogen or alkyl,

-$CONR'R''$ wherein R' and R'' are the same or different and each represent aryl, heteroaryl, hydrogen or alkyl, -Z-$NR'''R''''$ and -$NR'''R''''$ wherein Z is alkyl or alkenyl and R''' and R'''' are the same or different and each represent aryl, heteroaryl, hydrogen, alkyl or -CO-L wherein L is an alkyl or aryl group, and -O-Z-R''''' wherein Z is as defined above and R''''' is aryl, heteroaryl or heterocyclyl.

Typically, R in the moiety -$S(O)_2R$ is hydrogen or alkyl. Typically, R''' and R'''' in the moieties -Z-$NR'''R''''$ and -$NR'''R''''$ are the same or different and are hydrogen, alkyl, -CO-alkyl or -CO-phenyl. Preferably, at least one of R''' and R'''' is hydrogen or alkyl. Typically, Z is alkyl, for example methyl. Typically, R''''' in the moiety -O-Z-R''''' is heteroaryl, for example thiazolyl.

A preferred aryl substituent is phenyl. Preferred heteroaryl and heterocyclic substituents are 5- or 6- membered heteroaryl or heterocyclic groups containing 1, 2 or 3 heteroatoms selected from N, O and S. Examples include 5- or 6- membered rings containing 1, 2 or 3 heteroatoms, for example pyridyl, isoxazolyl, isothiazolyl, pyrazolyl, thiadiazolyl and oxadiazolyl. Other preferred substituents include nitro, hydroxy, halogen, for example chlorine, bromine and fluorine, C_1-C_4 haloalkyl such as -CF_3 and -CCl_3, C_1-C_4 alkyl, -CO_2R wherein R is hydrogen or C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, for example -$OCCl_3$ and -OCF_3, -$S(O)_2$-C_1-C_4 alkyl, -$CONR'R''$ wherein R' and R'' are the same or different and are heteroaryl or, preferably, aryl, hydrogen or C_1-C_4 alkyl, -$NR'''R''''$ wherein R''' and R'''' are the same or different and each represent hydrogen, alkyl or -CO-alkyl, and -O-alkyl-R''''', wherein R''''' is heteroaryl, for example thiazolyl.

The above substituents are themselves preferably unsubstituted or substituted by one or more further substituents selected from nitro, cyano, halogen, alkyl, for example haloalkyl, alkythio, alkoxy, for example haloalkoxy, and hydroxy. Typically, these further substituents are themselves unsubstituted.

An aryl group may optionally be fused to a further said aryl group or to a carbocyclic, heterocyclic or heteroaryl group. For example, it may be fused to a

pyridine ring to form a quinoline group, to a thiadiazole ring, for example a 1,2,5-thiadiazole ring to form an isobenzo[1,2,5]-thiadiazole group, or to a 1,4 dioxane or 1,3 dioxolane ring.

As used herein, a heteroaryl group is typically a 5- to 10- membered aromatic ring, such as a 5- or 6- membered ring, containing at least one heteroatom selected from O, S and N. Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrazolidinyl, pyrrolyl, oxadiazolyl, isoxazyl, thiadiazolyl, thiazolyl, imidazolyl and pyrazolyl groups. Thienyl groups are preferred. A heteroaryl group may be unsubstituted or substituted at any position. Typically, it carries 1, 2 or 3 substituents. Suitable substituents include aryl, for example phenyl, carbocyclyl, heteroaryl, heterocyclyl, cyano, nitro, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy, hydroxy, $-CO_2R$ and $-S(O)_2R$ wherein R is aryl, heteroaryl, hydrogen or alkyl, $-CONR'R''$ wherein R' and R'' are the same or different and each represent aryl, heteroaryl, hydrogen or alkyl, $-Z-NR'''R''''$ and $-NR'''R''''$ wherein Z is alkyl or alkenyl and R''' and R'''' are the same or different and each represent aryl, heteroaryl, hydrogen, alkyl or -CO-L wherein L is an alkyl or aryl group, and $-O-Z-R'''''$ wherein Z is as defined above and R''''' is aryl, heteroaryl or heterocyclyl.

Typically, R in the moiety $-S(O)_2R$ is hydrogen or alkyl. Typically, R''' and R'''' in the moieties $-Z-NR'''R''''$ and $-Z-NR'''R''''$ are the same or different and are hydrogen, alkyl, -CO-alkyl or -CO-phenyl. Preferably at least one of R''' and R'''' is hydrogen or alkyl. Typically, Z is alkyl, for example methyl. Typically, R''''' in the moiety $-O-Z-R'''''$ is heteroaryl, for example thiazolyl.

A preferred aryl substituent is phenyl. Preferred heteroaryl and heterocyclic substituents are 5- or 6- membered heteroaryl or heterocyclic groups containing 1, 2 or 3 heteroatoms selected from N, O and S. Examples include 5- or 6- membered rings containing 1, 2 or 3 heteroatoms, for example isoxazolyl, pyridyl imidazolyl, thiazolyl, isothiazolyl, pyrazolyl and thiadiazolyl. Other preferred substituents include nitro, halogen such as chlorine, bromine or fluorine, C_1-C_4 haloalkyl such as $-CF_3$ and $-CCl_3$, C_1-C_4 alkyl, $-CO_2R$ wherein R is hydrogen or C_1-C_4 alkyl, C_1-C_4 alkoxy, $-S(O)_2$-C_1-C_4 alkyl and $-(C_1$-C_4 alkyl)$-NR'''R''''$ wherein R''' and

$R^{////}$ are the same or different and each represent hydrogen, alkyl or -CO-aryl, for example -CO-phenyl.

The above substituents are themselves preferably unsubstitued or substituted by one or more further substituents selected from nitro, cyano, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy, and hydroxy. Typically, these further substituents are themselves unsubstituted.

A heteroaryl group may optionally be fused to a said aryl group, to a further heteroaryl group or to a heterocyclic or carbocyclic group. Examples of such fused heteroaryl groups include, for example, a thiophene ring fused to an imidazolyl group.

As used herein, a halogen is typically chlorine, fluorine, bromine or iodine and is preferably chlorine, fluorine or bromine.

As used herein, a said alkoxy group is typically a said alkyl group attached to an oxygen atom. An alkylthio group is typically a said alkyl group attached to a thio group. A haloalkyl or haloalkoxy group is typically a said alkyl or alkoxy group substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkyl and haloalkoxy groups include perhaloalkyl and perhaloalkoxy groups such as $-CX_3$ and $-OCX_3$ wherein X is a said halogen atom. Particularly preferred haloalkyl groups are CF_3 and CCl_3. Particularly preferred haloalkoxy groups are $-OCF_3$ and $-OCCl_3$.

As used herein, a carbocyclic group is a non-aromatic saturated or unsaturated hydrocarbon ring, typically having from 3 to 6 carbon atoms. Preferably it is a saturated hydrocarbon ring (i.e. a cycloalkyl group) having from 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is preferably cyclohexyl. A carbocyclic group may be unsubstituted or substituted at any position. Suitable substituents include nitro, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy, hydroxy, $-CO_2R$ and $-S(O)_2R$ wherein R is hydrogen or alkyl, cyano, and $-NR'R''$ and $-CONR'R''$ wherein R' and R'' are the same or different and each represent hydrogen or alkyl. Preferred substituents are nitro, halogen such as chlorine, bromine or fluorine, C_1-C_4 haloalkyl such as $-CF_3$ and $-CCl_3$, C_1-C_4 alkyl, $-CO_2R$ wherein R is hydrogen or C_1-C_4 alkyl,

C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, for example $-OCCl_3$ and $-OCF_3$, and $-S(O)_2$-C_1-C_4 alkyl. The above substituents are typically themselves unsubstituted.

As used herein, a heterocyclic group is typically a non-aromatic, saturated or unsaturated C_5-C_{10} carbocyclic ring in which one or more, for example 1, 2 or 3, of the carbon atoms are replaced by a heteroatom selected from N, O and S. Saturated heterocyclic groups are preferred. Examples of suitable heterocyclic groups include piperidine, morpholine, 1,4 dioxane and 1,3 dioxolane.

A heterocyclic group may be unsubstituted or substituted at any position. Suitable substituents include nitro, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy, hydroxy, $-CO_2R$ and $-S(O)_2R$ wherein R is hydrogen or alkyl, cyano, and $-NR'R''$ and $-CONR'R''$ wherein R' and R'' are the same or different and each represent hydrogen or alkyl. Preferred substituents are nitro, halogen such as chlorine, bromine or fluorine, C_1-C_4 haloalkyl such as $-CF_3$ and $-CCl_3$, C_1-C_4 alkyl, $-CO_2R$ wherein R is hydrogen or C_1-C_4 alkyl, C_1-C_4 alkoxy and $-S(O)_2$-C_1-C_4 alkyl. The above substituents are typically themselves unsubstituted.

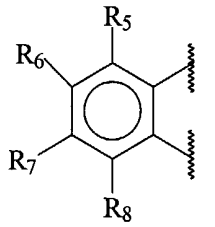
Typically, the groups $-NR_1S(O)_2R_3$ and $-NR_2S(O)_2R_4$ are attached to adjacent carbon atoms on the Ar moiety. When Ar is a heteroaryl group it is typically a pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl group. Preferably, Ar is an aryl group, in particular a phenyl group or a naphthyl group. Typically, it is unsubstituted or carries 1, 2, 3 or 4 substituents, preferably 1 or 2 substituents. Preferred substituents include aryl, heteroaryl, heterocyclyl, cyano, nitro, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy, hydroxy, $-CO_2R$ wherein R is aryl, heteroaryl, or, preferably, hydrogen or alkyl, and $-NR'R''$ and $-CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl. These substituents are preferably unsubstituted or substituted by one or more further substituent selected from nitro, cyano, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy and hydroxy. Typically, these further substituents are themselves unsubstituted.

Typically, at least one of R' and R'' in the moieties $-NR'R''$ and $-CONR'R''$ is hydrogen or alkyl. A preferred aryl substituent is phenyl. Preferred heteroaryl and heterocyclic substituents are 5- or 6- membered heteroaryl or

heterocyclic groups containing 1, 2 or 3 heteroatoms selected from N, O and S, for example oxadiazolyl groups. Further preferred substituents on the group Ar include hydroxyl nitro, cyano, halogen such as chlorine, fluorine and bromine, C_1-C_4 haloalkyl, C_1-C_4 alkyl, -CO_2R wherein R is hydrogen or C_1-C_4 alkyl, C_1-C_4 alkoxy and -CONR′R″ wherein R′ and R″ are the same or different and are aryl, heteroaryl, hydrogen or C_1-C_4 alkyl.

When Ar is an aryl group fused to an aryl, cycloalkyl, heterocyclic or heteroaryl group, it is typically fused to a said heterocyclic group. Preferably, it is fused to a saturated heterocyclic group containing, as heteroatoms, 2 oxygen atoms, for example 1,4 dioxane or 1,3 dioxolane.

More preferably, Ar is a group of formula Ar′



(Ar′)

wherein R_5 to R_8 are the same or different and represent aryl, heteroaryl, heterocyclyl, cyano, nitro, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy, hydroxy, -CO_2R wherein R is aryl, heteroaryl, hydrogen or alkyl, or -NR′R″ or -CONR′R″ wherein R′ and R″ are the same or different and are aryl, heteroaryl, hydrogen or alkyl, or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together form an alkylenedioxy group or, together with the carbon atoms to which they are attached, form a phenyl moiety.

Typically, R_5 to R_8 are the same or different and represent cyano, nitro, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy, hydroxy, -CO_2R wherein R is aryl, heteroaryl, hydrogen or alkyl, or -NR′R″ or -CONR′R″ wherein R′ and R″ are the same or different and are aryl, heteroaryl, hydrogen or alkyl, or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together form an

alkylenedioxy group or, together with the carbon atoms to which they are attached, form a phenyl moiety.

Typically, R in the moiety $-CO_2R$ is hydrogen or alkyl. Typically, R' and R'' in the moiety $-NR'R''$ are the same or different and are hydrogen or alkyl. Typically, R' and R'' in the moiety $-CONR'R''$ are the same or different and are hydrogen, alkyl or aryl.

Typically, R_5 and R_8 are the same or different and represent hydrogen, halogen, for example bromine, alkyl, hydroxy, alkoxy or $-NR'R''$ wherein R' and R'' are the same or different and are hydrogen or alkyl, and R_6 and R_7 are the same or different and represent hydrogen, halogen, for example, bromine, aryl, for example phenyl, heteroaryl, for example oxadiazolyl, heterocyclyl, nitro, cyano, halogen, alkyl, for example haloalkyl, alkoxy, for example haloalkoxy, alkylthio, hydroxy, $-CO_2R$ wherein R is aryl, heteroaryl, hydrogen or alkyl, or $-NR'R''$ or $-CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, or R_6 and R_7 together form an alkylenedioxy group such as a methylenedioxy or ethylenedioxy group or, together with the carbon atoms to which they are attached, form a phenyl moiety.

Typically, R_5 and R_8 are the same or different and represent hydrogen, alkyl, hydroxy, alkoxy or $-NR'R''$ wherein R' and R'' are the same or different and are hydrogen or alkyl, and R_6 and R_7 are the same or different and represent hydrogen, nitro, cyano, halogen, alkyl, haloalkyl, alkoxy, alkylthio, haloalkoxy, hydroxy, $-CO_2R$ wherein R is aryl, heteroaryl, hydrogen or alkyl, or $-NR'R''$ or $-CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, or R_6 and R_7 together form an alkylenedioxy group such as a methylenedioxy or ethylenedioxy group or, together with the carbon atoms to which they are attached, form a phenyl moiety.

Typically, R' and R'' in the $-NR'R''$ moiety are the same or different and are hydrogen or alkyl. Typically R' and R'' in the moiety $-CONR'R''$ are the same or different and are hydrogen, alkyl or aryl.

Preferably, at least one of R_5 and R_8 is hydrogen. More preferably,

one of R_5 and R_8 is hydrogen and the other is halogen or, preferably, hydrogen or hydroxy. More preferably still, both R_5 and R_8 are hydrogen.

Typically, R_5 to R_8 are unsubstituted or substituted by one or more further substituent selected from nitro, cyano, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy, and hydroxy. Typically, these further substituents are themselves unsubstituted.

Preferably, R_6 and R_7 represent hydrogen, aryl, for example phenyl, heteroaryl, for example oxadiazolyl, nitro, cyano, alkyl, alkoxy, haloalkyl, halogen, -CO_2H, -CO_2-alkyl or -$CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, or R_6 and R_7 together form a said alkylenedioxy group or a phenyl moiety. More preferably, R_6 and R_7 represent hydrogen, heteroaryl, for example oxadiazolyl, nitro, cyano, C_1-C_4 alkyl such as methyl or ethyl, halogen such as chlorine, fluorine or bromine, -CO_2-(C_1-C_4 alkyl) such as -CO_2-Et and -CO_2-Me, C_1-C_4 alkoxy such as -OMe, or -$CONR'R''$ wherein R' and R'' are the same or different and are heteroaryl, or, preferably, aryl, for example phenyl, hydrogen or C_1-C_4 alkyl, or R_6 and R_7, together with the carbon atoms to which they are attached, form a further phenyl moiety. More preferably still, R_6 and R_7 are the same or different and are selected from hydrogen, oxadiazolyl, chlorine, fluorine, bromine, nitro, cyano, methyl, methoxy, -CO_2H, -CO_2Et, -CO_2Me, -$CONH_2$, -CONHMe and -$CONMe_2$, -CONH-phenyl, -CONH-(4-trifluoromethoxyphenyl) or -CONH-(3,5-dimethoxyphenyl), or R_6 and R_7, together with the carbon atoms to which they are attached, form a further phenyl moiety.

When R_1 and/or R_2 is an alkyl group it is typically an unsubstituted alkyl group. Preferably, R_1 and R_2 are the same or different and are hydrogen or alkyl or R_1 and R_2 together from a C_1-C_3 alkylene group. More preferably, R_1 and R_2 are both hydrogen.

Typically, R_3 and R_4 are not simultaneously -alkynyl-aryl or -alkynyl-heteroaryl groups. Preferred -alkyl-aryl and -alkyl-heteroaryl groups are -(C_1-C_4-alkyl)-aryl and -(C_1-C_4 alkyl)-heteroaryl groups, for example -(C_1-C_4 alkyl)-phenyl groups such as benzyl groups. Preferred -alkenyl-aryl and -alkenyl-heteroaryl groups are -(C_2-C_4 alkenyl)-aryl and -(C_2-C_4 alkenyl)-heteroaryl groups, for example

-ethenyl-aryl groups such as -ethenyl-phenyl groups.

Typically, R_3 and R_4 are the same or different and each represent an aryl or heteroaryl group. Preferred aryl and heteroaryl groups include phenyl, naphthyl, pyridyl, furanyl, thienyl, imidazolyl, pyrazolidinyl, isoxazolyl and pyrrolyl groups. More preferred aryl and heteroaryl groups are phenyl, naphthyl, furanyl, thienyl and isoxazolyl groups.

When R_3 or R_4 contains an aryl or heteroaryl moiety which is fused to an aryl, cycloalkyl, heterocyclic or heteroaryl group, it is typically fused to a said heterocyclic group or to a said heteroaryl group. Examples of such fused groups include (1,2-cyclo(3-thioethyl)-imidazoyl, benzothienyl, indole and quinoline groups. Quinoline groups are preferred.

Typically, R_3 and R_4 are unsubstituted or carry 1, 2, 3 or 4 substituents, preferably 1 or 2 substituents. Preferred substituents include aryl, heteroaryl and heterocyclic groups, alkyl, haloalkyl, halogen, nitro, $-S(O)_2$-alkyl, haloalkoxy, cyano, $-CO_2R$ wherein R is aryl, heteroaryl, hydrogen or alkyl, alkoxy, hydroxy, $-CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, $-Z-NR'''R''''$ and $-NR'''R''''$ wherein Z is alkyl or alkenyl and R''' and R'''' are the same or different and each represent aryl, heteroaryl, hydrogen, alkyl or -CO-L wherein L is an alkyl or aryl group, and $-O-Z-R'''''$ wherein Z is as defined above and R''''' is aryl, heteroaryl or heterocyclyl.

Typically, Z is alkyl, for example methyl, in the above moieties. Typically, R''' and R'''' in the moieties $-Z-NR'''R''''$ and $-NR'''R''''$ are the same or different and are hydrogen, alkyl, -CO-alkyl or -CO-phenyl. Preferably, at least one of R''' and R'''' is hydrogen or alkyl. Typically, R''''' in the moiety $-O-Z-R'''''$ is heteroaryl, for example thiazolyl.

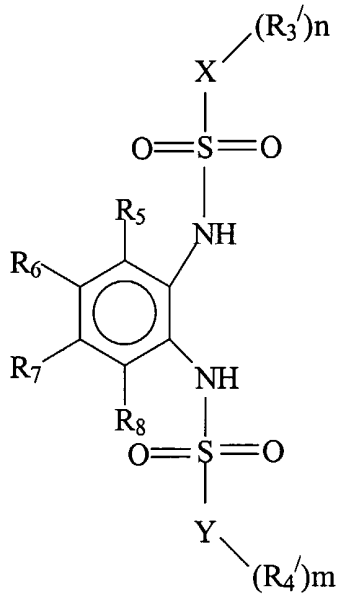
More typically, R_3 and R_4 are unsubstituted or carry 1, 2, 3 or 4 substituents, preferably 1 or 2 substituents selected from aryl, heteroaryl and heterocyclic groups, alkyl, haloalkyl, halogen, nitro, $-S(O)_2$-alkyl, haloalkoxy, cyano, $-CO_2R$ wherein R is aryl, heteroaryl, hydrogen or alkyl, alkoxy, hydroxy and $-NR'R''$ and $-CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl.

A preferred aryl substituent is phenyl. Preferred heteroaryl and heterocyclic substituents are 5- or 6- membered heteroaryl or heterocyclic groups containing 1, 2 or 3 heteroatoms selected from N, O and S. Examples include 5- or 6- membered rings containing 1, 2 or 3 heteroatoms, for example pyridyl, isoxazolyl, thiadiazolyl, thiazolyl, isothiazolyl and pyrazolyl. Other preferred substituents include C_1-C_4 alkyl such as methyl, ethyl, n-propyl, i-propyl or t-butyl, C_1-C_4 haloalkyl, halogen, nitro, cyano, C_1-C_4 alkoxy such as methoxy, -$S(O)_2$-C_1-C_4 alkyl, -$NR'''R''''$ wherein R''' and R'''' are the same or different and each represent hydrogen, C_1-C_4 alkyl, or -CO-(C_1-C_4 alkyl), -(C_1-C_4 alkyl)-$NR'''R''''$ wherein R''' and R'''' are the same or different and each represent hydrogen, C_1-C_4 alkyl or -CO-aryl, for example -CO-phenyl, and -O-(C_1-C_4 alkyl)-R''''', wherein R''''' is heteroaryl, for example thiazolyl.

Most preferred substituents are phenyl, methyl, trifluoromethyl, chlorine, fluorine, bromine, methoxy, trifluoromethoxy, nitro, cyano, -$S(O)_2$-Me, isoxazolyl, isothiazolyl, pyrazolyl, thiadiazolyl, pyridyl, thiazolyl, -NH-CO-Me, -O-CH_2-thiazolyl, -CH_2-NH-phenyl and -CH_2-NH-(4-chlorophenyl).

The above substituents are themselves preferably unsubstituted or substituted by one or more further substituents selected from nitro, cyano, halogen, alkyl, for example haloalkyl, alkylthio, alkoxy, for example haloalkoxy and hydroxy. Typically, these further substituents are themselves unsubstituted.

Further preferred compounds of the invention are compounds of formula (Ia)



(Ia)

wherein R_5 to R_8 are as defined above in the formula Ar', X and Y are the same or different and represent phenyl or thienyl, n represents an integer of from 0 to 4 when X is phenyl and an integer of from 0 to 3 when X is thienyl, m represents an integer of from 0 to 4 when Y is phenyl and an integer of from 0 to 3 when Y is thienyl, and R_3' and R_4' are the same or different and are selected from aryl, heteroaryl and heterocyclic groups, alkyl, for example haloalkyl, halogen, nitro, -$S(O)_2$-alkyl, alkoxy, for example haloalkoxy, cyano, -CO_2R wherein R is aryl, heteroaryl, hydrogen or alkyl, hydroxy, -$CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, -Z-$NR'''R''''$ and -$NR'''R''''$ wherein Z is alkyl or alkenyl and R''' and R'''' are the same or different and each represent aryl, heteroaryl, hydrogen, alkyl or -CO-L wherein L is an alkyl or aryl group, or -O-Z-R''''' wherein Z is as defined above and R''''' is aryl, heteroaryl or heterocyclyl.

Typically, Z is alkyl, for example methyl, in the above moieties. Typically, R''' and R'''' in the moieties -Z-$NR'''R''''$ and -$NR'''R''''$ are the same or different and are hydrogen, alkyl, -CO-alkyl or -CO-phenyl. Preferably, at least one of R''' and R'''' is hydrogen or alkyl. Typically, R''''' in the moiety -O-Z-R''''' is heteroaryl, for example thiazolyl.

Typically R_3' and R_4' are the same or different and are selected from heteroaryl and heterocyclic groups, alkyl, for example haloalkyl, halogen, nitro, -$S(O)_2$-alkyl, alkoxy, for example haloalkoxy, cyano, -CO_2R wherein R is aryl, heteroaryl, hydrogen or alkyl, hydroxy and -$NR'R''$ and -$CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl.

Preferred compounds of formula (Ia) are those in which one of R_5 and R_8 is hydrogen and the other is hydrogen, halogen or hydroxy, or in which R_5 and R_8 are both hydrogen, R_6 and R_7 are the same or different and are selected from aryl, for example phenyl, heteroaryl, for example oxadiazolyl, nitro, cyano, alkyl for example methyl and ethyl, haloalkyl, halogen, for example chlorine, fluorine and bromine, hydrogen, -CO_2H, -CO_2-alkyl for example -CO_2-Et and -CO_2-Me, alkoxy, for example methoxy and $CONR'R''$ wherein R' and R'' are the same or different and are heteroaryl, or, preferably, aryl, hydrogen or alkyl, or R_6 and R_7 together form an alkylenedioxy group such as a methylenedioxy or ethylenedioxy group or, together with the carbon atoms to which they are attached, form a further phenyl moiety, X and Y are the same or different and are phenyl or thienyl, n and m are the same or different and are 0, 1 or 2 and R_3' and R_4' are the same or different and are selected from:

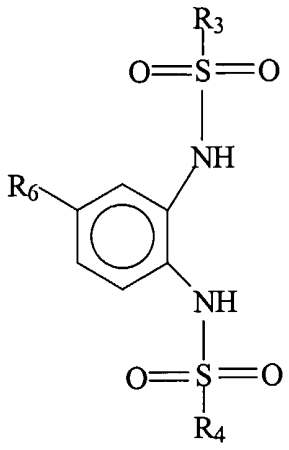
(a) when attached to a phenyl moiety, aryl, for example phenyl, C_1-C_4 alkyl, for example methyl, ethyl, n-propyl, i-propyl or t-butyl, C_1-C_4 haloalkyl, for example CCl_3 and CF_3, halogen, for example chlorine, fluorine and bromine, nitro, cyano, C_1-C_4 alkoxy, for example methoxy, -CO_2R wherein R is hydrogen or C_1-C_4 alkyl, -$NR'R''$ wherein R' and R'' are the same or different and are hydrogen, C_1-C_4 alkyl or -CO-(C_1-C_4 alkyl), -O-(C_1-C_4 alkyl)-R''' wherein R''' is heteroaryl, for example thiazolyl, or heterocyclyl, and -$S(O)_2$-C_1-C_4 alkyl; and

(b) when attached to a thienyl moiety, pyridyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, nitro, halogen such as chlorine, bromine or fluorine, C_1-C_4 haloalkyl such as -CF_3 and -CCl_3, C_1-C_4 alkyl such as methyl, ethyl, n-propyl, i-propyl or t-butyl, -CO_2R wherein R is hydrogen or C_1-C_4 alkyl, C_1-C_4 alkoxy such as methoxy, -(C_1-C_4 alkyl)-NH-aryl, for example -(C_1-C_4 alkyl)-NH-phenyl, and -$S(O)_2$-C_1-C_4 alkyl.

Typically, in these preferred compounds, R_6 and R_7 are the same or different and are selected from nitro, alkyl such as methyl or ethyl, haloalkyl, halogen such as chlorine, fluorine or bromine, hydrogen, -CO_2-alkyl such as -CO_2-Et and -CO_2-Me, alkoxy such as methoxy and -CONR'R'' wherein R' and R'' are the same or different and are aryl, heteroaryl, or, preferably, hydrogen or alkyl, or R_6 and R_7 together form an alkylenedioxy group such as a methylenedioxy or ethylenedioxy group or, together with the carbon atoms to which they are attached, form a further phenyl moiety. Typically, when attached to a phenyl moiety, R_3' and R_4' are selected from C_1-C_4 alkyl, for example methyl, ethyl, n-propyl, i-propyl or t-butyl, C_1-C_4 haloalkyl, for example CCl_3 and CF_3, halogen, for example chlorine, fluorine and bromine, nitro, C_1-C_4 alkoxy, for example methoxy, and -$S(O)_2$-C_1-C_4 alkyl. Typically, when attached to a thienyl moiety, R_3' and R_4' are selected from isoxazolyl, isothiazolyl, pyrazolyl, nitro, halogen, for example chlorine, bromine and fluorine, C_1-C_4 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_4 alkyl, for example methyl, ethyl, n-propyl, i-propyl and t-butyl, -CO_2R wherein R is hydrogen or C_1-C_4 alkyl, C_1-C_4 alkoxy, for example methoxy, and -$S(O)_2$-C_1-C_4 alkyl.

Particularly preferred compounds of the formula (Ia) are those in which R_5 and R_8 are hydrogen, R_6 and R_7 are the same or different and are selected from hydrogen, oxadiazolyl, chlorine, fluorine, bromine, nitro, cyano, methyl, methoxy, -CO_2Et, -CO_2Me, -$CONH_2$, -CONHMe, -$CONMe_2$, -CONH-phenyl, -CONH-(4-trifluromethoxyphenyl) and -CONH-(3,5-dimethoxyphenyl) or, together with the carbon atoms to which they are attached, form a phenyl moiety, n and m are the same or different and are 0, 1 or 2, X and Y are the same or different and are phenyl or thienyl and R_3' and R_4' are the same or different and are selected from methyl, ethyl, i-propyl, chlorine, fluorine, bromine, methoxy, trifluoromethoxy, nitro, cyano, -$S(O)_2$Me, -CO_2H, -NH-CO-CH_3, -O-CH_2-(2-chlorothiazolyl) and, when X and Y are thienyl, pyridyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl and -CH_2-NH-R wherein R is phenyl or 4-chlorophenyl.

Compounds of the invention which are more preferred are compounds of formula (Ib)and salts thereof.



(Ib)

wherein R_3 and R_4 are the same or different and are selected from (a) phenyl optionally substituted by halogen, for example chlorine, C_1-C_4 alkyl, for example methyl, C_1-C_4 haloalkyl, for example -CF_3 or C_1-C_4 haloalkoxy, for example -OCF_3 and (b) thienyl, optionally substituted by halogen, for example chlorine, C_1-C_4 alkyl, for example methyl, C_1-C_4 haloalkyl, for example -CF_3 and C_1-C_4 haloalkoxy, for example -OCF_3, and R_6 is halogen, for example chlorine and fluorine, or C_1-C_4 haloalkoxy, for example -CF_3 and -CCl_3.

Compounds of the formula (I) containing one or more chiral centre may be used in enantiomerically or diasteroisomerically pure form, or in the form of a mixture of isomers.

Typically, when the compounds of the invention are used as antibacterial agents, for example to inhibit a strain of *staphylococcus aureus* other than MRSA, R_3 and R_4 are not phenyl groups substituted at the para position by an amino group. More typically, in such compounds R_3 and R_4 are not 4-aminophenyl or 4-nitrophenyl groups. Preferably, R_3 and R_4 are not aminophenyl groups in such compounds.

Preferably, when R_3 and R_4 are simultaneously phenyl groups substituted at the para position with a C_1-C_4 alkyl group such as a methyl group, Ar is not a group of formula Ar', as defined above, wherein R_5, R_7 and R_8 are hydrogen and R_6 is C_1-C_4 alkyl such as methyl or -CO_2-(C_1-C_4 alkyl) such as -CO_2-Et.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutical acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines or heterocyclic amines.

Particularly preferred compounds of formula (I) include:

1,2-Bis(4-nitrophenylsulfonylamino)-benzene

1,2-Bis(4-methylphenylsulfonylamino)-4,5-dibromobenzene

3,4-Bis(4-methylphenylsulfonylamino)-6-bromotoluene

1,2-Bis(4-methylphenylsulfonylamino)-4-fluorobenzene

3-(3-trifluoromethylphenylsulfonylamino)-4-(4-iodophenylsulfonylamino)toluene

1,2-Bis(4-methylphenylsulfonylamino)-4-nitrobenzene

3-(4-methylphenylsulfonylamino)-4-(4-chlorophenylsulfonylamino)toluene

1,2-Bis(4-methylphenylsulfonylamino)-benzene

1,2-Bis(4-methylphenylsulfonylamino)-4-fluoro-5-nitrobenzene

3,4-Bis(4-methylphenylsulfonylamino)-benzoic acid methyl ester

1,2-Bis(4-bromophenylsulfonylamino)-benzene

N,N-1,4-bis(4-methylphenylsulfonamdio)-7,8-dibromoquinazoline

1,2-Bis(4-methylphenylsulfonylamino)-4,5-dichlorobenzene

2,3-Bis(4-methylphenylsulfonylamino)naphthalene

1,2-Bis(4-methylphenylsulfonylamino)-4,5-difluorobenzene

1,2-Bis(4-bromophenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(4-fluorophenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(3-bromophenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-benzene

1,2-Bis(4-isopropylphenylsulfonylamino)-benzene

1,2-Bis(4-fluorophenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(4-methylphenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(4-isopropylphenylsulfonylamino)-4,5-dimethylbenzene

2,3-Bis(4-fluorophenylsulfonylamino) phenol

2,3-Bis(4-methylphenylsulfonylamino) phenol

2,3-Bis(4-trifluoromethoxyphenylsulfonylamino) phenol

2,3-Bis(4-isopropylphenylsulfonylamino) phenol

3,4-Bis(4-fluorophenylsulfonylamino) anisole

3,4-Bis(4-methylphenylsulfonylamino) anisole

3,4-Bis(4-fluoromethoxyphenylsulfonylamino) anisole

3,4-Bis(4-isopropylphenylsulfonylamino) anisole

3,4-Bis(4-methylsulfonphenylsulfonylamino) anisole

1,2-Bis(phenylsulfonylamino) benzene

1,2-Bis(3-trifluoromethylphenylsulfonylamino) benzene

1,2-Bis(4-trifluoromethylphenylsulfonylamino) benzene

1,2-Bis(3-chloro-2-methylphenylsulfonylamino) benzene

1,2-Bis(2,6-difluorophenylsulfonylamino) benzene

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(3-chloro-2-methylphenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(2,6-difluorophenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(2,6-difluorophenylsulfonylamino)-4-fluorobenzene

2,3-Bis(3,4-dichlorophenylsulfonylamino)-phenol

2,3-Bis(2,4-difluorophenylsulfonylamino)-phenol

1,2-Bis(4-trifluoromethylphenylsulfonylamino)-4,5-dimethylbenzene

2,3-Bis(5-chloro,2-methoxyphenylsulfonylamino)-phenol

3,4-Bis(4-trifluoromethylphenylsulfonylamino)-benzoic acid ethyl ester

3,4-Bis(3,4-dichlorophenylsulfonylamino) anisole

3,4-Bis(5-chloro,2-methoxyphenylsulfonylamino) anisole

1,2-Bis(4-fluorophenylsulfonylamino) benzene

1,2-Bis(2,4-difluorophenylsulfonylamino) benzene

1,2-Bis(phenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(5-chloro-2-methoxyphenylsulfonylamino)-4,5-dimethylbenzene

2,3-Bis(phenylsulfonylamino)-phenol

2,3-Bis(2-methyl-5-nitrophenylsulfonylamino) phenol

3,4-Bis(3-trifluoromethylphenylsulfonylamino) anisole

1,2-Bis(5-chloro-2-methoxyphenylsulfonylamino) benzene

2,3-Bis(4-trifluoromethylphenylsulfonylamino) phenol

3,4-Bis(4-trifluoromethylphenylsulfonylamino) anisole

1,2-Bis(4-trifluoromethylphenylsulfonylamino)-4-fluorobenzene

3,4-Bis(3-trifluoromethylphenylsulfonylamino)-benzoic acid ethyl ester

1,2-Bis(2-thienylsulfonylamino)-benzene

2,3-Bis(2-thienylsulfonylamino)-phenol

1,2-Bis(2-chloro-5-thienylsulfonylamino)-napthalene

1,2-Bis[2-(3-oxazolyl)-5-thienylsulfonylamino)-napthalene

3,4-Bis(2-chloro-5-thienylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(2-thienylsulfonylamino)fluorobenzene

2,3-Bis(2-chloro-5-thienylsulfonylamino) phenol

3,4-Bis(2-chloro-5-thienylsulfonylamino)-benzoic acid ethyl ester

3,4-Bis(2-thienylsulfonylamino)-anisole

2,3-Bis(2-chloro-5-thienylsulfonylamino)-benzene

1,2-Bis[2-(3-oxazolyl)-5-thienylsulfonylamino)-benzene

1,2-Dimethyl-4,5-bis(2-thienylsulfonylamino)-benzene

1,2-Dimethyl-4,5-bis(2-chloro-5-thienylsulfonylamino)-benzene

1,2-Difluoro-4,5-bis(2-thienylsulfonylamino)-benzene

1,2-Dibromo-4,5-bis(2,3-dichloro-5-thienylsulfonylamino)-benzene

3,4-Bis(2-thienylsulfonylamino)chlorobenzene

3,4-Bis(5-chloro-2-thienylsulfonylamino)chlorobenzene

3,4-bis(2-thienylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(2-chloro-5-thienylsulfonylamino)fluorobenzene

1,2-Bis(2-thienylsulfonylamino)-3,4,5,6-tetramethylbenzene

3,4-bis(2-thienylsulfonylamino)-benzoic acid ethyl ester

1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-phenol

1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-anisole

1,2-Dibromo-4,5-bis(2,5-dichloro-3-thienylsulfonylamino)-benzene

3,4-Bis(2,5-dichloro-3-thienylsulfonylamino)chlorobenzene

1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-3,4,5,6-tetramethylbenzene

2,3-Bis(phenylsulfonylamino)naphthalene

2,3-Bis(3-trifluoromethylphenylsulfonylamino)naphthalene

2,3-Bis(4-trifluoromethoxyphenylsulfonylamino)naphthalene

2,3-Bis(3,4-dichlorophenylsulfonylamino)naphthalene

2,3-Bis(4-isopropylphenylsulfonylamino)naphthalene

2,3-Bis(4-trifluoromethyphenylsulfonylamino)naphthalene

2,3-Bis(2,4diflurophenylsulfonylamino)naphthalene

2,3-Bis(2-chloro-5-thienylsulfonylamino)naphthalene

2,3-Bis(2-methyl-4-nitrophenylsulfonylamino)naphthalene

2,3-Bis(2-methyl-3-chlorophenylsulfonylamino)naphthalene

2,3-Bis(4-cyanophenylsulfonylamino)naphthalene

2,3-Bis(3,5dimethyl-3-oxazoylsulfonylamino)naphthalene

2,3-Bis(2-aza-4,5-benzothiazoylsulfonylamino)naphthalene

2,3-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)naphthalene

2,3-Bis(2,6-difluorophenylsulfonylamino)naphthalene

2,3-Bis(3-nitro-4-methylphenylsulfonylamino)naphthalene

3,4-Bis(2-(1,2-cyclo(3-thioethyl)-4-chloro-5-imidazoylsulfonylamino)naphthalene

2,3-Bis(4-methylsulfonophenylsulfonylamino)naphthalene

1,2-Bis(4-fluorophenylsulfonylamino)-4-nitrobenzene

3,4-Bis(4-fluorophenylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(4-trifluoromethylphenylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(2-chloro-5-thienylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(2-methoxy-2-chlorophenylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(4-methyl-2-nitrophenylsulfonylamino)-benzoic acid methyl ester

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene

1,2-Bis(2-thienylsulfonylamino)-4-fluorobenzene

1,2-Bis(3,4-dichlorophenylsulfonylamino)-4-fluorobenzene

1,2-Bis(2-methyl-5-nitrophenylsulfonylamino)-4-fluorobenzene

1,2-Bis(phenylsulfonylamino)-4,5-difluorobenzene

3,4-Bis(3,4-dichlorophenylsulfonylamino)-benzoic acid ethyl ester

3,4-Bis(2,4-dichlorophenylsulfonylamino)-benzoic acid ethyl ester

3,4-Bis(2-chloro-5-thienylsulfonylamino)-benzoic acid ethyl ester

3,4-Bis(2-methyl,5-nitrophenylsulfonylamino)-benzoic acid ethyl ester

3,4-Bis(2,6-difluorophenylsulfonylamino)-benzoic acid ethyl ester

1,2-Bis(2-methyl,5-nitrophenylsulfonylamino)-4-methoxybenzene

1,2-Bis(4-methyl,3-nitrophenylsulfonylamino)-4-methoxybenzene

1,2-Bis(3,4-dichlorophenylsulfonylamino)-benzene

1,2-Bis(2-chloro-5-thienylsulfonylamino)-benzene

1,2-Bis(2-methyl-5-nitrophenylsulfonylamino)-benzene

1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-benzene

1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-benzene

1,2-Bis(4-isopropylphenylsulfonylamino)-4-nitrobenzene

1,2-Bis(2-thienylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(3,4-dichlorophenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(2-chloro-5-thienylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(2-methyl-5-nitrophenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(4-methylsulfonophenylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(1-naphthylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(2,3-dichloro-5-thienylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(4-nitrophenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(4-biphenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(4-bromophenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(4-carboxyphenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(3,4-dimethoxyphenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(3-methylphenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(2-fluorophenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(2-methoxyphenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(4-methylphenylsulfonylamino)-4-cyanobenzene

1,2-Bis(phenylsulfonylamino)-4-chlorobenzene

1,2-Bis(4-fluorophenylsulfonylamino)-4-chlorobenzene

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene

1,2-Bis(3-trifluoromethoxyphenylsulfonylamino)-4-chlorobenzene

1,2-Bis(2-thienylsulfonylamino)-4-chlorobenzene

1,2-Bis(3,4-dichlorophenylsulfonylamino)-4-chlorobenzene

1,2-Bis(4-isopropylphenylsulfonylamino)-4-chlorobenzene

1,2-Bis(2,4-difluorophenylsulfonylamino)-4-chlorobenzene

3,4-Bis(4-chloro-2methoxyphenylsulfonylamino)-benzoic acid ethyl ester

1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4-chlorobenzene

1,2-Bis(2-chloro-5-thienylsulfonylamino)-4-chlorobenzene

1,2-Bis(2-methyl-5-nitrophenylsulfonylamino)-4-chlorobenzene

1,2-Bis(2-methyl-3-chlorophenylsulfonylamino)-4-chlorobenzene

1,2-Bis(4-cyanophenylsulfonylamino)-4-chlorobenzene

1,2-Bis(3,5-dimethyl-4-oxazoylsulfonylamino)-4-chlorobenzene

1,2-Bis(2,6-difluorophenylsulfonylamino)-4-chlorobenzene

1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-4-chlorobenzene

3,4-Bis(2,4-difluorophenylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(2-methyl-5-nitrophenylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(2-methyl-3-chlorophenylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(2,6difluorophenylsulfonylamino)-benzoic acid methyl ester

1,2-Bis(2-chloro-5-thienylsulfonylamino)-4-fluorobenzene

1,2-Bis(2-methyl-3-chlorophenylsulfonylamino)-4-fluorobenzene

1,2-Bis(2-methoxy-5-chlorophenylsulfonylamino)-4-fluorobenzene

1,2-Bis(2-methyl-3-chlorophenylsulfonylamino)-3,4,5,6-tetramethylbenzene

3,4-Bis(2-thienylsulfonylamino)-benzoic acid ethyl ester

3,4-Bis(3-chloro-2-methylphenylsulfonylamino)-benzoic acid ethyl ester

2,3-Bis(4-fluorophenylsulfonylamino)naphthalene

1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-benzene

3,4-Bis(3-trifluoromethylphenylsulfonylamino)-benzoic acid methyl ester

1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4-fluorobenzene

1,2-Bis(2-(1,2-cyclo(3-thioethyl)-4-chloro-5-imidazoylsulfonylamino)-4-fluorobenzene

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4,5-difluorobenzene

1,2-Bis(3-chloro-2-methylphenylsulfonylamino)-4,5-difluorobenzene

1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-4,5-difluorobenzene

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-chloro-5-methylbenzene

2,3-Bis(2-thienylsulfonylamino)naphthalene

1,2-Bis(4-trifluoromethylphenylsulfonylamino)-4-chlorobenzene

1,2-Bis(4-fluorophenylsulfonylamino)-4,5-difluorobenzene

1,2-Bis(4-methylsulfonophenylsulfonylamino)-3,4,5,6-tetramethylbenzene

1,2-Bis(4-isopropylphenylsulfonylamino)-4-fluorobenzene

1,2-Bis(4-cyanophenylsulfonylamino)-4-fluorobenzene

1,2-Bis(4-methylphenylsulfonylamino)-4-cyanobenzene

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4,5dibromobenzene

1,2-Bis(2-trifluoromethoxyphenylsulfonylamino)-3,5dibromobenzene

1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4,5dibromobenzene

3,4-Bis(8-quinolylsulfonylamino)-benzoic acid ethyl ester

1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4-fluorobenzene

1,2-Bis(phenylsulfonylamino)-4-fluorobenzene

3,4-Bis(3,5-dimethyl-4-oxazoylsulfonylamino)-benzoic acid methyl ester

3,4-Bis(4-isopropylphenylsulfonylamino)-benzoic acid methyl ester

1,2-Bis(4-methylphenylsulfonylamino)-4-chlorobenzene

1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4,5-dimethylbenzene

3,4-Bis(3,5-dimethyl-4-oxazoylsulfonylamino)-4,5-difluorobenzoate

1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4-methoxybenzene

1,2-Bis(2-(1,2-cyclo(3-thioethyl)-4-chloro-5-imidazoylsulfonylamino)-4-methoxybenzene

1,2-Bis(phenylsulfonylamino)-4-cyanobenzene

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-cyanobenzene

1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4-cyanobenzene

1,2-Bis(2-thienylsulfonylamino)-4-cyanobenzene

1,2-Bis(4-isopropylphenylsulfonylamino)-4-cyanobenzene

1,2-Bis(2,4-difluorophenylsulfonylamino)-4-cyanobenzene

1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4-cyanobenzene

1,2-Bis(3-chloro,2-methylphenylsulfonylamino)-4-cyanobenzene

1,2-Bis(2,6-difluorophenylsulfonylamino)-4-cyanobenzene

1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4,5-difluorobenzene

1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(2-thienylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(3,4-dichlorophenylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(4-trifluoromethylphenylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(2,4-difluorophenylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(2,5-dichloro,3-thienylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(2-chloro,5-thienylsulfonylamino)-4-chloro-5-methylbenzene

3,4-Bis(2,4-dimethyl,5-oxa-3-thiazoylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(2-aza-4,5-benzothiazoylsulfonylamino)4-chloro-5-methylbenzene

1,2-Bis(2-(5-oxa-2-thiazoyl)-5-thienylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(2,4-difluorophenylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(4-methyl,3-nitrophenylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(4-methyl,3-nitrophenylsulfonylamino)-4-cyanobenzene

1,2-Bis(phenylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(3-chloro,4-acetamidophenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(4-acetamidophenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(5-(2-pyridyl)-2-thienylsulfonylamino)-4-chlorobenzene

1,2-Bis(5-(4-chloroacetamidomethyl)-2-thienylsulfonylamino)-4-chlorobenzene

1,2-Bis(2-(2-aza-4-thiazoyl)-5-thienylsulfonylamino)-4-chlorobenzene

1,2-Bis(2-(2-methyl-4-thiazoyl)-5-thienylsulfonylamino)-4-chlorobenzene

3,4-Bis(4-methylphenylsulfonylamino)-benzoic acid

2,3-Bis(2,4-dichlorophenylsulfonylamino)naphthalene

1,2-Bis(2,4-dichlorophenylsulfonylamino)-benzene

1,2-Bis(2-(2-methyl-4-thiazoyl)-5-thienylsulfonylamino)-benzene

1,2-Bis(2-(2-methyl-4-thiazoyl)-5-thienylsulfonylamino)-4,5-dimethylbenzene

1,2-Bis(2-(2-methyl-4-thiazoyl)-5-thienylsulfonylamino)-4-fluorobenzene

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-(3-methyl-5-oxadiazole) benzene

1-(4-methylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene

1-(2,5-dichloro-3-thienylsulfonylamino)-2-(3-trifluoromethylsulfonylamino)-benzene

3,4-Bis(4-methylphenylsulfonylamino)-*N*-phenyl-benzamide

3,4-Bis(4-methylphenylsulfonylamino)-*N*-(4-fluoromethoxyphenyl) benzamide

3,4-Bis(4-methylphenylsulfonylamino)-*N*-(3,5-dimethoxyphenyl) benzamide

3-(4-methylphenylsulfonylamino)-4-(3-trifluoromethylphenylsulfonylamino)-benzoic acid methyl ester

3-(2,5-dichloro-3-thienylsulfonylamino)-4-(3-trifluoromethylsulfonylamino)-benzoic acid methyl ester

1,2-Bis(4-methoxyphenylsulfonylamino)-4,5-dibromobenzene

1,2-Bis(4-methoxyphenylsulfonylamino)-4,5-dichlorobenzene

1-(4-methoxyphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene

1-(3-chlorophenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene

1-(2-chlorophenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene

1-(3-methylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene

1-(4-methylamidomethylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene

1-(2-(phenylamidomethyl)-5-thienylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene

1-(4-(2-chloro-5-thiazoylmethoxyphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene

1-(2-(phenylamidomethyl)-5-thienylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-benzene

1-(2-(phenylamidomethyl)-5-thienylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene

1,2-Bis(2-(*N*-phenyl)amidomethyl-5-thienylsulfonylamino)-benzene

1-(4-(2-chloro-5-thiazoylmethoxyphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-benzene

1-(4-(2-chloro-5-thiazoylmethoxyphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene

1-(2-chlorophenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-benzene

1-(2-chlorophenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene

1-(2-methylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-benzene

1-(3-methylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene

1-(4-trifluoromethylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-benzene

1,2-Bis(benzylsulfonylamino)-4,5-diflurobenzene

1,2-Bis(benzylsulfonylamino)-benzene

1,2-Bis(benzylsulfonylamino)-4-chloro-5-methylbenzene

1,2-Bis(phenylstyrylsulfonylamino)-4-chlorobenzene

1-(3-trifluoromethylsulfonylamino)-2-(phenylstyrylsulfonylamino)-4-fluorobenzene

1-(3-trifluoromethylsulfonylamino)-2-(phenylstyrylsulfonylamino)-benzene

1-(3-trifluoromethylsulfonylamino)-2-(benzylsulfonylamino)-4-fluorobenzene

4-(3-trifluoromethylsulfonylamino)-3-(2-phenylethenylsulfonylamino)-benzoic acid ethyl ester

and salts thereof, in particular pharmaceutically acceptable salts thereof.

Compounds which are particularly effective are

1,2-Bis (2,5-dichloro-3-thienylsulfonylamino)-4-chlorobenzene,

1,2-Bis (4-trifluoromethoxyphenylsulfonylamino)-4-chlorobenzene,

1,2-Bis (3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene,

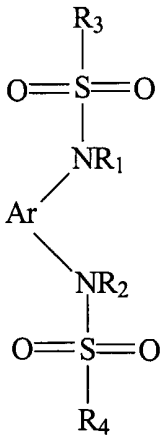
1,2-Bis (2-chloro-5-thienylsulfonylamino)-4-chlorobenzene,

1,2-Bis (2-chloro-5-thienylsulfonylamino)-4-fluorobenzene,

1,2-Bis(2-methyl-3-chlorophenylsulfonylamino)-4-fluorobenzene,

and salts thereof, in particular pharmaceutically acceptable salts thereof.

Certain bissulfonamide derivatives of the formula (I) are novel per se. These compounds are bissulfonamides of the formula (1d), and salts thereof,



(Id)

wherein:

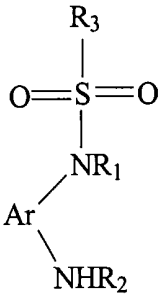
- R_1 and R_2 are as defined above;
- R_3 and R_4 are as defined above and
- Ar is a group of formula Ar', as defined above,

provided that when R_1 and R_2 are both hydrogen, and Ar is an unsubstituted napthyl group, a phenanthracene group or a phenyl group optionally substituted by 1 or 2 dimethylmethylenedioxy, hydroxy, methoxy, ethoxy, methyl, chlorine, bromine, fluorine, nitro, CF_3 or amino groups, R_3 and R_4 are not (a) unsubstituted quinoline groups, (b) unsubstituted phenyl groups, (c) phenyl groups monosubstituted by a methyl, methoxy, $-CO_2H$, chlorine, cyano, nitro or amino group, or by a group $-O-CO-N(CH_3)-$ or (d) phenyl groups disubstituted by a nitro group and a methyl group.

Suitable salts include these mentioned above as examples of pharmaceutically acceptable salts.

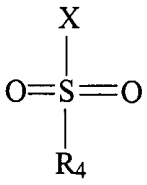
Preferred novel compounds of the invention are bissulfonamides of the formula (Id), as defined above, and salts thereof, wherein, when R_1 and R_2 are both hydrogen and Ar is an unsubstituted napthyl group, a phenanthracene group or a phenyl group optionally substituted by 1 or 2 C_1-C_4 alkylenedioxy, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkyl, halogen, nitro, C_1-C_4 haloalkyl or amino groups, R_3 and R_4 are not unsubstituted quinoline groups or phenyl groups optionally substituted by 1 or 2 groups selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, -CO_2R wherein R is hydrogen or C_1-C_4 alkyl, halogen, cyano, nitro and amino groups, and from groups of the formula -O-CO-N(C_1-C_4 alkyl)-.

The compounds of formula (I) may be prepared by a process comprising reacting a compound of formula (II)



(II)

wherein Ar, R_1, R_2 and R_3 are as defined above, with a compound of formula (III)



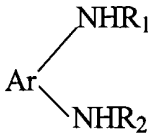
(III)

wherein R_4 is as defined above and X is a leaving group such as a chlorine atom.

Typically, the reaction takes place in the presence of an organic solvent and a base. Typically, the base is pyridine, triethylamine or

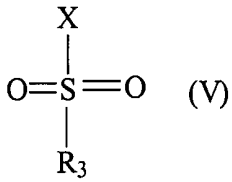
4-dimethylaminopyridine. Typically, the solvent is acetonitrile, dichloromethane, toluene or dimethylformamide. Typically, molar equivalents of the compounds of formulae (II) and (III) are used.

A compound of formula II may be prepared by reacting a compound of formula (IV).



(IV)

wherein Ar, R_1 and R_2 are as defined above, with a compound of formula (V)



(V)

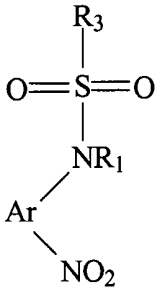
wherein R_3 and X are as defined above.

Typically, the reaction takes place in the presence of an organic solvent and a base. Typically the solvent is acetonitrile, dichloromethane, toluene or dimethylformamide. Typically the base is pyridine, triethylamine or 4-dimethylaminopyridine. Typically, molar equivalents of compounds of formulae (IV) and (V) are used.

Compounds of formula I wherein R_3 and R_4 are the same may, of course, be prepared by reacting a compound of formula (IV) with two molar equivalents of a compound of formula (III) under the reaction conditions set out above.

Preferably the solvent used in the above reactions is acetonitrile or dichloromethane and the reactions take place in the presence of pyridine or 4-dimethylaminopyridine.

Alternatively, compounds of formula (II), in which Ar, R_1, and R_3 are as defined above and R_2 is hydrogen, can also be prepared by reaction of a compound of formula (VI) with a suitable reducing agent.

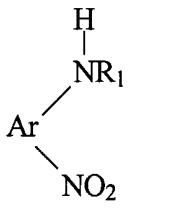


(VI)

wherein Ar, R_1 and R_3 are as defined above.

Typically the reducing agent is palladium on carbon with hydrazine hydrate, tin (II) chloride, platinum on carbon with hydrogen gas or ferric chloride in alkaline solution. Preferably the reducing agent is tin (II) chloride or palladium on carbon with hydrazine hydrate. The reaction can be carried out in an organic solvent such as ethanol, dimethylformamide, chloroform, ethyl acetate or tetrahydrofuran. Preferably the solvent is dimethylformamide or ethanol.

Compounds of formula (VI) can be prepared by reaction of a compound of formula (VII),



(VII)

wherein Ar and R_1 are as defined above, with a compound of formula (V). Typically, the reaction takes place in the presence of an organic solvent and a base. Typically the solvent is acetonitrile, dichloromethane, toluene or dimethylformamide. Typically the base is pyridine, triethylamine or 4-

dimethylaminopyridine. Typically, molar equivalents of compounds of formulae (IV) and (V) are used

Further synthetic manipulation of the thus obtained compounds of formula (I), such as bromination, nitration and acylation may be carried out by conventional methods to achieve further compounds of formula I.

The thus obtained bissulfonamide derivatives of formula (I) may be salified by treatment with an appropriate acid or base.

Compounds of formulae (III), (IV), (V), (VI) and (VII) are known compounds, or may be prepared by analogy with known methods.

The compounds of formula (I) are found to be inhibitors of dehydroquinate synthetase enzymes, in particular AroB, and type II dehydroquinase enzymes, in particular AroQ.

As explained above, dehydroquinate synthetase enzymes invariably form an essential part of the shikimate pathway. Further, type II dehydroquinase enzymes have been implicated in the shikimate pathway in many organisms. Type II dehydroquinase enzymes also form an important part of the catabolic pathway by which quinic acid catabolism is effected. The compounds of the invention are particularly highly active against organisms in which the shikimate pathway involves a type II dehydroquinase enzyme and organisms using both the shikimate pathway and the quinic acid catabolic pathway. That is because they have two enzyme targets in such organisms.

The present invention thus provides a method for treating a patient in need of an inhibitor of the biosynthesis of aromatic amino acids via the shikimate pathway which method comprises administering to said patient an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The shikimic acid pathway is essential for the synthesis of aromatic amino acids in fungi and bacteria. Accordingly, the compounds of the invention are effective in treating or preventing bacterial or fungal infection. Indeed, the compounds of the invention are effective against many bacteria which have developed resistance to conventional antibiotics. For example, they are effective against Methicillin Resistant *Staphylococcus Aureus* (MRSA). Accordingly, the said

medicament is typically for use in treating or preventing, and the said patient is typically suffering from or susceptible to, a bacterial or fungal attack. In particular, the said patient is typically suffering from or susceptible to, and the said medicament is typically for use in the prevention or treatment of, a MRSA infection.

The gene encoding type II dehydroquinase has been observed in *Actinobacillus pleuropneumoniae, Actinobacillus actinomycetes, Aeromonas salmonicida subsp. Salmonicida, Amycolatopsis mediterranei, Bacillus subtilis, Corynebacterium glutamicum, Corynebacterium pseudotuberculosis, Emericella nidulans, Haemophilus influenzae, Helicobacter pylori, Neurospora crassa, Pseudomonas aeruginosa, Streptomyces coelicolor, Streptomyces lavendulae, Synechocystis sp, Thermotoga meritima, Campylobacter jejuni, Clostridium acetobutylicum, Porphyromonas gingivalis, Deinococcus radiodurans, Chlorobium tepidum, Vibrio cholerae, Yersinia pestis, Shewanella putrafaciens, Thiobacillus ferroxidans, Synechocystis PCC6803, Candida albicans, Bordetella pertussis, Mycobacterium avium, Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium leprae, Caulobacter eresentus* and *Klebsiella pneumoniae*.

The compounds of the present invention are particularly active against the above organisms. This is because, as explained above, the compounds of the invention act to inhibit both dehydroquinate synthetase and Type II dehydroquinase enzymes in these organisms. Accordingly, the said medicament is typically for use in the treatment or prevention of, or the said patient is typically suffering from or susceptible to, attack by one of the above organisms.

The compounds of the invention can also be used generally to prevent bacterial growth. For example, they may be added to solutions, such as solutions for contact lenses, to prevent bacterial growth. They may also be used in antibiotic coatings on surgical instruments and in products such as medicated soaps. Accordingly, the present invention also provides the non-therapeutic use of a compound of the invention in inhibiting bacterial growth. Also provided is a contact lens solution or a medicated soap comprising a compound of the invention. Further, the present invention provides a surgical instrument having thereon an antibiotic coating comprising a compound of the invention.

The shikimic acid pathway is also implicated in the

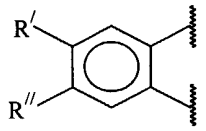
metabolism of parasites. For example, it is implicated in the treatment of apicomplexan parasites. Accordingly, the compounds of the invention are effective in the treatment or prevention of infection by a parasite in which the biosynthesis of aromatic amino acids is effected via the shikimic pathway. Such parasites can be identified, for example, by (a) determining whether *in vitro* growth is inhibited by well characterised inhibitors of the shikimate pathway such as glyphosphate, and (b) determining whether such inhibition is reversed by addition of p-aminobenzoate. Parasites whose *in vitro* growth is inhibited by glyphosphate and in which such inhibition is reversed by addition of p-aminobenzote use the shikimate pathway in their metabolic processes. The compounds of the invention will therefore be active against such parasites.

In particular, the compounds of the invention are active against apicomplexan parasites, for example *Toxoplasma gondii, Cryptosporidium parvum and Plasmodium falciparum*. *Plasmodium falciparum* is known to cause malaria. Thus, the said patient is typically suffering from or susceptible to, and the said medicament is typically for use in the treatment or prevention of, infection by an apicomplexan parasite. In particular, the said patient is typically suffering from or susceptible to, and the said medicament is typically for use in the treatment or prevention of, malaria.

When used for treating the above disorders, the compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

Certain compounds of the formula (I) have not previously been disclosed in a therapeutic context. Accordingly, the present invention also provides a bissulfonamide derivative of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, for use in a method of treating the human or animal body,

wherein Ar, R_1, R_2, R_3 and R_4 are as defined above, provided that, when R_1 and R_2 are hydrogen and R_3 and R_4 are phenyl, 4-methylphenyl or 4-aminophenyl, Ar is not



wherein R′ and R″ are methyl or chlorine.

The present invention also provides a pharmaceutical composition containing such a bissulfonamide derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

A compound of the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a

natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

A therapeutically effective amount of a compound of the invention is administered to a patient. A typical dose is from about 0.001 to 50 mg per kg of body weight, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated, the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

The shikimic acid pathway is also essential in higher plants, algae and fungi. Further, the pathway for the catabolism of quinic acid is also found in fungi. The compounds of the invention are therefore effective in controlling higher plants, algae and fungi. They can be used as selective herbicides and fungicides, for example. Accordingly, the present invention provides the use of a compound of formula (I), or an agriculturally acceptable salt thereof, as a herbicide or a fungicide. Also provided is a method of controlling weeds or fungi at a locus, which method comprises treating the locus with a compound of formula (I) or an agriculturally acceptable salt thereof.

Typically the locus comprises agricultural or horticultural plants or a medium in which such plants grow.

A preferred method of controlling fungi is a method of treating a plant for, or protecting a plant against, fungal attack, which method comprises applying to the plant a compound of formula (I) or an agriculturally acceptable salt thereof. Smuts and rusts on a plant can, for example, be treated by this method.

Typically, the active compound is applied to the leaves. The number of applications and the rate of application depend on the intensity of the fungal

attack. However, an active compound can also be applied to a plant through the roots via the soil (systemic action) by impregnating the locus of the plant with a liquid composition comprising the active compound, or by applying the compound in solid form to the soil, e.g. in granular form (soil application). The active compound may also be applied to seeds (coating) by impregnating the seeds either with a liquid formulation containing the active compound, or coating them with a solid formulation. In special cases, further types of application are also possible, for example, selective treatment of the plant stems or buds.

The present invention also provides a herbicidal or fungicidal composition comprising a novel bissulfonamide derivative, as defined above, or an agriculturally acceptable salt thereof and an agriculturally acceptable carrier or diluent.

Suitable agriculturally acceptable salts include those salts mentioned above as examples of pharmaceutically acceptable salts.

The said herbicidal or fungicidal composition may be prepared by mixing a compound of formula (I), or an agriculturally acceptable salt thereof, with an agriculturally acceptable carrier or diluent. Suitable such compositions include wettable powders, granules, water-dispersible granules, emulsion concentrates, suspension concentrates, and powders suitable for dusting plants. The fungicidal or herbicidal compositions may comprise further agricultural chemicals, for example further fungicides and herbicides or insecticides, miticides, plant growth regulators, fertilizers and soil conditioners.

The herbicidal or fungicidal composition preferably comprises a further fungicide or herbicide. This leads not only to a reduction in dose and manpower, but also to broadening of the herbicidal or fungicidal spectrum. This broadening is attributable to cooperative activities.

Suitable agriculturally acceptable carriers and diluents include solid or liquid carriers and diluents.

Examples of the solid carriers or diluents include clays such as kaolinites, montmorillonites, illites and polygroskites, more specifically pyrophyllite, attapulgite, sepiolite, kaolinite, bentonite, vermiculite, mica and talc. Other

inorganic substances such as gypsum, calcium carbonate, dolomite, diatomaceous earth, magnesium lime, phosphorus lime, zeolite, silicic anhydride and synthetic calcium silicate may also be used. Suitable organic carriers and diluents include soybean flour, tobacco flour, walnut flour, wheat flour, wood flour, starch and crystalline cellulose. Further synthetic or natural polymers such as coumarone resin, petroleum resin, alkyd resin, polyvinyl chloride, polyalkylene glycol, ketone resin, ester gum, copal gum and dammar gum are suitable, as are waxes such as carnauba wax and bee wax.

Examples of suitable liquid carriers and diluents include paraffin or naphthene hydrocarbons such as kerosene, mineral oil, spindle oil and white oil, aromatic hydrocarbons such as xylene, ethylbenzene, cumene and methylnaphthalene, chlorinated hydrocarbons such as trichloroethylene, monochlorobenzene and o-chlorotoluene, ethers such as dioxane and tetrahydrofuran, ketones such as acetone, methyl ethyl ketone, diisobutyl ketone, cyclohexanone, acetophenone and isophorone, esters such as ethyl acetate, amyl acetate, ethylene glycol acetate, diethylene glycol acetate, dibutyl maleate and diethyl succinate, alcohols such as methanol, n-hexanol, ethylene glycol, diethylene glycol, cyclohexanol and benzyl alcohol, ether alcohols such as ethylene glycol ethyl ether and diethylene glycol butyl ether and polar solvents such as dimethylformamide, dimethyl sulfoxide and water.

Typically the herbicidal and fungicidal compositions comprise a surfactant and/or another auxiliary agent suitable for various purposes such as emulsification, dispersion, humidification, spreading, dilution, combination destruction control, stabilization of active ingredients, improvement of flowability, prevention of corrosion and prevention of freezing. Preferably, the herbicidal and fungicidal compositions of the invention comprise at least one surfactant. The present invention also provides a herbicidal or fungicidal composition comprising:

- a bissulfonamide of formula (I) or an agriculturally acceptable salt thereof;
- at least one surfactant; and
- an agriculturally acceptable carrier or diluent.

Suitable surfactants include nonionic, anionic, cationic and amphoteric surfactants. Nonionic and anionic surfactants are preferred.

Suitable anionic surfactants can be both water-soluble soaps and water-soluble synthetic surface-active compounds.

Suitable soaps are the alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts of higher fatty acids (chains of 10 to 22 carbon atoms), for example the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures which can be obtained for example from coconut oil or tallow oil. The fatty acid methyltaurin salts may also be used.

More frequently, however, so-called synthetic surfactants are used, especially fatty sulfonates, fatty sulfates, sulfonated benzimidazole derivatives or alkylarylsulfonates.

The fatty sulfonates or sulfates are usually in the form of alkali metal salts, alkaline earth metal salts or unsubstituted or substituted ammonium salts and have a C_8 to C_{22} alkyl radical which also includes the alkyl moiety of alkyl radicals, for example, the sodium or calcium salt of lignonsulfonic acid, of dodecylsulfate or of a mixture of fatty alcohol sulfates obtained from natural fatty acids. These compounds also comprise the salts of sulfuric acid esters and sulfonic acids of fatty alcohol/ethylene oxide adducts. The sulfonated benzimidazole derivatives preferably contain 2 sulfonic acid groups and one fatty acid radical containing 8 to 22 carbon atoms. Examples of alkylarylsulfonates are the sodium, calcium or triethanolamine salts of dodecylbenzenesulfonic acid, dibutylnapthalenesulfonic acid, or of a naphthalenesulfonic acid/formaldehyde condensation product. Also suitable are corresponding phosphates, e.g. salts of the phosphoric acid ester of an adduct of p-nonylphenol with 4 to 14 moles of ethylene oxide.

Non-ionic surfactants are preferably polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, or saturated or unsaturated fatty acids and alkylphenols, said derivatives containing 3 to 30 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenols.

Further suitable non-ionic surfactants are the water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediamine propylene glycol and alkylpolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which

adducts contain 20 to 250 ethylene glycol ether groups and 10 to 100 propylene glycol ether groups. These compounds usually contain 1 to 5 ethylene glycol units per propylene glycol unit. Representative examples of non-ionic surfactants are nonylphenolpolyethoxyethanols, castor oil polyglycol ethers, polypropylene /polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethylene glycol and octylphenoxyethoxyethanol. Fatty acid esters of polyoxyethylene sorbitan and polyoxyethylene sorbitan trioleate are also suitable non-ionic surfactants.

Cationic surfactants are preferably quaternary ammonium salts which have, as N-substituents, at least one C_8-C_{22} alkyl radical and, as further substituents, lower unsubstituted or halogenated alkyl, benzyl or lower hydroxyalkyl radicals. The salts are preferably in the form of halides, methylsulfates or ethylsulfates, e.g. stearyltrimethylammonium chloride or benzyldi(2-chloroethyl)ethylammomium bromide.

The surfactants customarily employed in the art of formulation are described, for example, in McCutcheon's Detergents and Emulsifiers Annual, MC Publishing Corp. Ringwood, New Jersey, 1979, and Sisely and Wood, Encyclopaedia of Surface Active Agents, Chemical Publishing Co., Inc. New York, 1980.

The said auxiliary agent includes casein, gelatin, albumin, glue, sodium alginate, carboxymethylcellulose, methylcellulose, hydroyethylcellulose and polyvinyl alcohol.

The above-described carriers or diluents and various auxiliary agents may be used alone or in combination.

The content of active compound in the herbicidal and fungicidal composition of the invention may vary widely depending on the form of formulation. Typically, the amount of active compound is 0.1 to 99%, preferably 1 to 80% by weight of the composition.

More specifically, wettable powders typically contain 25 to 90% by weight of active compound. Granules typically contain 1 to 35% by weight of active compound, which may be mixed with the solid carrier or diluent uniformly, or mixed to or absorbed on the surface of the solid carrier or diluent uniformly. It is preferred that the diameter of the granules is from 0.2 to 1.5mm. Emulsion concentrates

typically contain 5 to 30% by weight of active compound, and in additional 5 to 20% by weight of an emulsifier. Suspension concentrates typically contain 5 to 50% by weight of active compound, and in addition 3 to 10% by weight of a dispersion wetting agent.

The compounds of the invention may be applied in effective amounts to various places to be protected, for example farm-lands such as paddy fields and upland, or non-crop lands. When used as herbicides they may be applied prior to germination of weeds or to weeds of various stages from after germination to growth period. When the compounds of the invention are used as herbicides, the dose is generally, as amount of active ingredients, on the order of 0.1 to 10,000 g/ha, preferably 1 to 5,000 g/ha, more preferably from 50 to 3,000 g/ha. The dose may be varied depending on the kind of objective weeds, their growth stages, places of application and weather. When the compounds of the invention are used as fungicides, the dose is typically from 50g to 5kg of active ingredient per hectare, preferably from 100g to 2kg per hectare, more preferably from 200g to 500g per hectare.

The shikimic acid pathway is also essential for the synthesis of aromatic amino acids in algae. Accordingly, the compounds of the present invention are effective in controlling algae. The present invention therefore provides the use of a compound of formula (I), or a salt thereof, in controlling algae. In particular, the invention provides a method of treating algae in a fish tank or pond, which method comprises applying to the fish tank or pond a compound of formula (I) or a salt thereof.

As explained above, type II dehydroquinase enzymes form an important part of the catabolic pathway by which quinic acid catabolism is effected. The present invention therefore also provides the use of a bissulfonamide derivative of the formula (I), as defined above, or a salt thereof, in the inhibition of quinic acid catabolism. Suitable salts include those given above as examples of pharmaceutically acceptable salts.

The catabolic pathway is found in many fungi and bacteria. The compounds of the invention are therefore typically used to inhibit the catabolism of quinic acid by a fungus or a bacterium. They may be formulated for such use as a herbicidal or fungicidal composition, as defined above, and used at the dosage ranges given above.

The following Examples illustrate the invention.

Example 1

1,2-Bis (3-nitrophenylsulfonylamino)-benzene

A solution of 1,2-phenylenediamine (10mM) in dry pyridine (50ml) was stirred under nitrogen at room temperature and 3-nitrobenzenesulfonyl chloride (20mM) was added portion-wise over a few minutes. The resulting solution was heated at reflux for 5hr then allowed to cool and poured onto cold 1N hydrochloric acid (500ml). The product was extracted into ethyl acetate (3x200ml) and the combined organic extracts washed with water, 1N sodium hydroxide, then water again before drying over anhydrous sodium sulfate and evaporating under reduced pressure. Column chromatography on silica provided the required product (3.1g, 65%).

Examples 2 to 8

The compounds set out below were prepared in the same way as in Example 1, using appropriate starting materials.

Example	Compound
2	3,4-Bis(4-methylphenylsulfonylamino)-6-bromotoluene
3	1,2-Bis(4-methylphenylsulfonylamino)-4-fluorobenzene
4	3,4-Bis-(phenylsulfonylamino)toluene
5	1,2-Bis-(methylphenylsulfonylamino)-4-nitrobenzene
6	3,4-Bis(4-methylphenylsulfonylamino)toluene
7	1,2-Bis(4-methylphenylsulfonylamino-4-fluoro-5-nitrobenzene
8	3,4-Bis(4-methylphenylsulfonylamino)-benzoic acid methyl ester

Example 9

1,2-Bis (4-toluenesulfonylamino)-benzene

A solution of 1,2-phenylenediamine (10mM, 1.08g) in dry acetonitrile (50ml) was stirred under nitrogen at room temperature. Diisopropylethylamine (5ml) was added, followed by benzenesulfonyl chloride (4.19g, 22mM). The resulting solution was heated at reflux for 10hr then cooled and evaporated under reduced pressure. The resulting solid was partitioned between water and chloroform and the organic layer separated, washed with 1N sodium hydroxide solution, then water, and finally dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane. The product was isolated as a white powder (1.8g, 43%) mpt 203-205°C.

Examples 10 to 21

The compounds set out below were prepared in the same way as in Example 9 using appropriate starting materials.

Example	Compound
10	1,2-Bis(3,5-ditrifluoromethylphenylsulfonylamino)-benzene
11	1,2-Bis(4-bromophenylsulfonylamino)-benzene
12	1,2-Bis(4-tert-butylphenylsulfonylamino)-benzene
13	1,2-Bis(4-methylphenylsulfonylamino)-4,5-methylenedioxybenzene
14	1,2-Bis(4-methylphenylsulfonylamino)-4,5-dichlorobenzene
15	1,2-Bis(4-methylphenylsulfonylamino)-4,5-ethylenedioxybenzene
16	2,3-Bis(4-methylphenylsulfonylamino)-naphthalene
17	1,2-Bis(4-methylphenylsulfonylamino)-4,5-difluorobenzene
18	1,2-Bis(4-bromophenylsulfonylamino)-4,5-dibromobenzene
19	1,2-Bis(4-chlorophenylsulfonylamino)-4,5-dibromobenzene
20	1,2-Bis(4-fluorophenylsulfonylamino)-4,5-dibromobenzene
21	1,2-Bis(3-bromophenylsulfonylamino)-4,5-dibromobenzene

Example 22

3-(3-trifluoromethylphenylsulfonylamino)-4-(4-methylphenylsulfonylamino)toluene

A solution of 3,4-diaminotoluene (10mM) in dry pyridine (50ml) was stirred under nitrogen at room temperature and 3-(3-trifluoromethylphenyl)sulfonyl chloride (10mM) was added portion-wise over a few minutes. The resulting solution was heated at reflux for 5hr then allowed to cool and poured onto cold water. The product was extracted into ethyl acetate (3x200ml) and the combined organic extracts washed with water, 1N sodium hydroxide, then water again before drying over anhydrous sodium sulfate and evaporating under reduced pressure. The resulting 4-(4-methylphenylsulfonylamino)-3-aminotoluene was subjected to the same reaction conditions, employing 3-(trifluoromethylphenyl)sulfonyl chloride (10mM). Column chromatography on silica provided the required product.

Examples 23 and 24

The compounds set out below were prepared in the same way as in Example 22, using appropriate starting materials.

Example	Compound
23	3-(4-chlorophenylsulfonylamino)-4-(4-methylphenylsulfonylamino)toluene
24	3-(4-fluorophenylsulfonylamino)-4-(4-methylphenylsulfonylamino)toluene

Example 25

1,2-Bis (4-toluenesulfonylamino)-4,5-dibromobenzene

A solution of 1,2-Bis (4-toluenesulfonylamino)-benzene (500mg, 1.2mM) in glacial acetic acid (10ml) was stirred and sodium acetate (200mg) added. Bromine (385mg, 0.13ml, 2.4mM) was added dropwise and the resulting dark solution then heated at 80°C for 3hr. Water (50ml) was added and the resulting precipitate isolated by filtration and purified by recrystallisation from acetic acid to give the required product as white needles, m.pt 213-215°C (650mg, 94%).

Example 26

N,N-1,4-Bis(4-methylphenylsulfonylamino)quinazoline

4,5-Dibromo-1,2-bis(4-methylphenylsulfonylamino) benzene (176mg, $3x10^{-4}$mol) and dibromoethane (57mg, $3x10^{-4}$mol) were refluxed with potassium carbonate (1.0g, 7.25 x 10^{-4}mol) in dry acetonitrile (250ml) for 4 hours under nitrogen and then stirred at RTP overnight. The solution was filtered and evacuated to dryness to yield the product as a light brown glass (0.16g, 89%).

Example 27

1,2-Bis(2-chloro,5-thienylsulfonylamino)-4-chloro-5-methylbenzene

4-chloro-5-methylphenylene-1,2-diamine (10mM, 1.56) was dissolved in dry pyridine (100ml) and stirred at room temperature under nitrogen. To this solution a solution of 5-chloro-2-thienylsulfonyl chloride (21mM, 4.55g) in pyridine (15 ml) is added and the resultant solution stirred at 85ºC for 18 hr under nitrogen. The solution was then poured into 0.5M cold dilute hydrochloric acid (125ml) and the product extracted into chloroform. The solution was then dried over anhydrous sodium hydrogen carbonate and evaporated under reduced pressure. The crude product was purified by column chromatography on silica eluting with a mixture of chloroform and methanol. the product was further purified by recrystallisation from

ethanol/water and the product dried overnight under vacuum. The product was obtained as an off white crystalline solid (2.18g, 42%).

Examples 28 to 58

The compounds set out below were prepared in the same way as in Example 27, using appropriate starting materials.

Example	Compound
28	2,3-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)naphthalene
29	1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-benzene
30	1,2-Bis(1-naphthylsulfonylamino)-4,5-dibromobenzene
31	1,2-Bis(2,3-dichloro-5-thienylsulfonylamino)-4,5-dibromobenzene
32	1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4,5-dibromobenzene
33	1,2-Bis(4-nitrophenylsulfonylamino)-4,5-dibromobenzene
34	1,2-Bis(4-biphenylsulfonylamino)-4,5-dibromobenzene
35	1,2-Bis(4-bromophenylsulfonylamino)-4,5-dibromobenzene
36	1,2-Bis(4-carboxyphenylsulfonylamino)-4,5-dibromobenzene
37	1,2-Bis(3,4-dimethoxyphenylsulfonylamino)-4,5-dibromobenzene
38	1,2-Bis(3-methylphenylsulfonylamino)-4,5-dibromobenzene
39	1,2-Bis(2-fluorophenylsulfonylamino)-4,5-dibromobenzene
40	1,2-Bis(2-methoxyphenylsulfonylamino)-4,5-dibromobenzene
41	2,3-Bis(4-fluorophenylsulfonylamino)naphthalene
42	1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4-fluorobenzene
43	1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4,5-dibromobenzene
44	1,2-Bis(2-trifluoromethoxyphenylsulfonylamino)-3,5-dibromobenzene
45	1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4,5-dibromobenzene
46	1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4,5-dimethylbenzene
47	1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4,5-dibromobenzene
48	1,2-Bis(3-chloro,4-acetamidophenylsulfonylamino)-4,5-dibromobenzene
49	1,2-Bis(4-acetamidophenylsulfonylamino)-4,5-dibromobenzene
50	1,2-Bis(5-(2-pyridyl)-2-thienylsulfonylamino)-4-chlorobenzene
51	1,2-Bis(5-(4-chloroacetamidomethyl)-2-thienylsulfonylamino)-4-chlorobenzene
52	1,2-Bis(2-(2-aza-4-thiazoyl)-5-thienylsulfonylamino)-4-chlorobenzene

53	1,2-Bis(2-(2-methyl-4-thiazoyl)-5-thienylsulfonylamino)-4-chlorobenzene
54	1,2-Bis(2-(2-methyl-4-thiazoyl)-5-thienylsulfonylamino)-4-fluorobenzene
55	1,2-Bis(4-methoxyphenylsulfonylamino),4,5-dibromobenzene
56	1,2-Bis(4-methoxyphenylsulfonylamino),4,5-dichlorobenzene.
57	1,2-Bis(2-(*N*-phenylamidomethyl)-5-thienylsulfonylamino)-benzene
58	1,2-Bis(2-phenylethenylsulfonylamino)-4-chlorobenzene

Example 59

1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-benzene

To a solution of 1,2 phenylenediamine (24 mg, 0.22 mmol) in acetonitrile (2 ml) was added pyridine (0.05 ml, 0.66 mmol, 3 equivalents). To this solution was added a solution of (4-trifluoromethoxy)phenylsulfonyl chloride (84 mg, 0.44 mmol) in acetonitrile (2 ml). The reaction mixture was left to stand at ambient temperature for twenty four hours. On completion the reaction mixture was concentrated *in vacuo* to afford a heavy syrup. The syrup was dissolved in dichloromethane (1 ml) and water (1 ml). The phases were separated and the organic phase was washed with water (1 ml), citric acid (10%, 1 ml) and saturated brine
(1 ml). The organic solution was dried in vacuo to afford the final product which was analysed by liquid chromatography in conjunction with mass spectrometry.

Examples 60 to 64

The compounds set out below were prepared in the same way as in Example 59, using appropriate starting materials.

Example	Compound
60	1,2-Bis(4-isopropylphenylsulfonylamino)-benzene
61	1,2-Bis(4-fluorophenylsulfonylamino)-4,5-dimethylbenzene
62	1,2-Bis(4-methylphenylsulfonylamino)-4,5-dimethylbenzene

63	1,2-Bis(3-trifluoromethoxyphenylsulfonylamino)-4,5-dimethylbenzene
64	1,2-Bis(4-isopropylphenylsulfonylamino)-4,5-dimethylbenzene

The above compounds were analysed by liquid chromatography, in conjunction with a mass spectrometer as detector. The equipment used was a Waters 2700 Sample Manager, with Waters 2690 Alliance Solvent Delivery System and Waters 996 Photodiode Array Detector. The mass spectrometer used was a Micromass Platform LCZ Mass Spectrometer running Micromass MassLynx Software, v3.2 build 004. Chromatography was carried out on a Waters Symmetry 3.5□m C18 50x2.0mm (WAT200650) column with a gradient elution from 5% 10mM formic acid in acetonitrile and 95% 10mM formic acid in water to 95% 10mM formic acid in acetonitrile and 5% 10mM formic acid in water over 3 minutes at 0.5ml/minute flow rate. UV detection was at 200-300nm and mass spectra were collected by positive and negative electrospray. All reaction products showed the desired compound with satisfactory purity.

Example 65

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4,5-dimethylbenzene

To a solution of 4,5-dimethyl-1,2-phenylenediamine (30 mg, 0.22 mmol) in acetonitrile (2 ml) was added pyridine (0.05 ml, 0.66 mmol, 3 equivalents). To this solution was added a solution of 3-trifluoromethylphenylsulphonylchloride (108 mg, 0.44 mmol) in dimethylformamide (2 ml). The reaction mixture was left to stand at ambient temperature for twenty four hours. On completion the reaction mixture was concentrated *in vacuo* to afford a heavy syrup. The syrup was dissolved in dichloromethane (1 ml) and water (1 ml). The phases were separated and the organic phase was washed with water (1 ml), citric acid (10%, 1 ml) and saturated brine (1 ml). The organic solution was dried in vacuo to afford the final product which was analysed by liquid chromatography in conjunction with mass spectrometry.

Examples 66 to 256

The compounds set out below were prepared in the same way as Example 65, using appropriate starting materials.

Example	Compound
66	2,3-Bis(4-methylphenylsulfonylamino)-phenol
67	2,3-Bis(4-trifluoromethoxyphenylsulfonylamino)-phenol
68	2,3-Bis(4-isopropylphenylsulfonylamino)-phenol
69	2,3-Bis(4-methylsulfonphenylsulfonylamino)-phenol
70	3,4-Bis(4-fluorophenylsulfonylamino)-anisole
71	3,4-Bis(4-methylphenylsulfonylamino)-anisole
72	3,4-Bis(4-trifluoromethoxyphenylsulfonylamino)-anisole
73	3,4-Bis(4-isopropylphenylsulfonylamino)-anisole
74	3,4-Bis[(4-methylsulfonyl)phenylsulfonylamino]anisole
75	1,2-Bis(3-trifluoromethylphenylsulfonylamino)-benzene
76	1,2-Bis(4-trifluoromethylphenylsulfonylamino)-benzene
77	1,2-Bis(3-chloro-2-methylphenylsulfonylamino)-benzene
78	1,2-Bis(2,6-difluorophenylsulfonylamino)-benzene
79	1,2-Bis(phenylsulfonylamino)-benzene
80	1,2-Bis(3-chloro-2-methylphenylsulfonylamino)-4,5-dimethylbenzene
81	1,2-Bis(2,6-difluorophenylsulfonylamino)-4,5-dimethylbenzene
82	1,2-Bis(2,6-difluorophenylsulfonylamino)-4-fluorobenzene
83	2,3-Bis(3-trifluoromethylphenylsulfonylamino)-phenol
84	2,3-Bis(3,4-dichlorophenylsulfonylamino)-phenol
85	2,3-Bis(2,4-difluorophenylsulfonylamino)-phenol
86	1,2-Bis(4-trifluoromethylphenylsulfonylamino)-4,5-dimethylbenzene
87	2,3-Bis(5-chloro,2-methoxyphenylsulfonylamino)-phenol
88	3,4-bis(4-trifluoromethylphenylsulfonylamino)-benzoic acid ethyl ester
89	3,4-Bis(3,4-dichlorophenylsulfonylamino)-anisole
90	3,4-Bis(5-chloro,2-methoxyphenylsulfonylamino)-anisole
91	1,2-Bis(4-fluorophenylsulfonylamino)-benzene
92	1,2-Bis(2,4-difluorophenylsulfonylamino)-benzene
93	1,2-Bis(phenylsulfonylamino)-4,5-dimethylbenzene
94	1,2-Bis(5-chloro,2-methoxyphenylsulfonylamino)-4,5-dimethylbenzene
95	2,3-Bis(phenylsulfonylamino)-phenol
96	2,3-Bis(2-methyl,5-nitrophenylsulfonylamino)-phenol
97	3,4-Bis(3-trifluoromethylphenylsulfonylamino)-anisole
98	1,2-Bis(5-chloro,2-methoxyphenylsulfonylamino)-benzene
99	2,3-Bis(4-trifluoromethylphenylsulfonylamino)-phenol
100	3,4-Bis(4-trifluoromethylphenylsulfonylamino)-anisole
101	1,2-Bis(4-trifluoromethylphenylsulfonylamino)-4-fluorobenzene
102	3,4-Bis(3-trifluoromethylphenylsulfonylamino)-benzoic acid ethyl ester
103	1,2-Bis(2-thienylsulfonylamino)-benzene
104	2,3-Bis(2-thienylsulfonylamino)-phenol

105 1,2-Bis(2-chloro-5-thienylsulfonylamino)-napthalene
106 1,2-Bis[2-(3-oxazolyl)-5-thienylsulfonylamino)-napthalene
107 3,4-Bis(2-chloro-5-thienylsulfonylamino)-benzoic acid methyl ester
108 3,4-Bis(2-thienylsulfonylamino)-fluorobenzene
109 2,3-Bis(2-chloro-5-thienylsulfonylamino)-phenol
110 3,4-Bis(2-chloro-5-thienylsulfonylamino)-benzoic acid methyl ester
111 3,4-Bis(2-thienylsulfonylamino)-anisole
112 2,3-Bis(2-chloro-5-thienylsulfonylamino)-benzene
113 1,2-Bis[2-(3-oxazolyl)-5-thienylsulfonylamino)-benzene
114 1,2-Dimethyl-4,5-bis(2-thienylsulfonylamino)-benzene
115 1,2-Dimethyl-4,5-bis(2-chloro-5-thienylsulfonylamino)-benzene
116 1,2-Difluoro-4,5-bis(2-thienylsulfonylamino)-benzene
117 1,2-Dibromo-4,5-Bis(2,3-dichloro-5-thienylsulfonylamino)-benzene
118 3,4-Bis(2-thienylsulfonylamino)-chlorobenzene
119 3,4-Bis(5-chloro-2-thienylsulfonylamino)-chlorobenzene
120 3,4-bis(2-thienylsulfonylamino)-benzoic acid methyl ester
121 3,4-Bis(2-chloro-5-thienylsulfonylamino)-fluorobenzene
122 1,2-Bis(2-thienylsulfonylamino)-3,4,5,6-tetramethylbenzene
123 3,4-bis(2-thienylsulfonylamino)-benzoic acid ethyl ester
124 1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4,5-dimethylbenzene
125 1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-anisole
126 1,2-Dibromo-4,5-bis (2,5-dichloro-3-thienylsulfonylamino)-benzene
127 2,3-Bis(4-isopropylphenylsulfonylamino)-phenol
128 1,2-Bis(2,5-dichlorothienyl-3-sulfonylamino)-4,5-dimethylbenzene
129 1,2-Bis(2,5-dichlorothienyl-3-sulfonylamino)-4-methoxybenzene
130 1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-3,4,5,6-tetramethylbenzene
131 2,3-Bis(phenylsulfonylamino)-naphthalene
132 2,3-Bis(3-trifluoromethylphenylsulfonylamino)-naphthalene
133 2,3-Bis(4-trifluoromethoxyphenylsulfonylamino)-naphthalene
134 2,3-Bis(3,4-dichlorophenylsulfonylamino)-naphthalene
135 2,3-Bis(4-isopropylphenylsulfonylamino)-naphthalene
136 2,3-Bis(4-trifluoromethyphenylsulfonylamino)-naphthalene
137 2,3-Bis(2,4diflurophenylsulfonylamino)-naphthalene
138 2,3-Bis(2-chloro-5-thienylsulfonylamino)-naphthalene
139 2,3-Bis(2-methyl-4-nitrophenylsulfonylamino)-naphthalene
140 2,3-Bis(2-methyl-3-chlorophenylsulfonylamino)-naphthalene
141 2,3-Bis(4-cyanophenylsulfonylamino)-naphthalene
142 2,3-Bis(3,5dimethyl-3-oxazoylsulfonylamino)-naphthalene
143 2,3-Bis(2-aza-4,5-benzothiazoylsulfonylamino)-naphthalene
144 2,3-Bis(2,6-difluorophenylsulfonylamino)-naphthalene
145 2,3-Bis(3-nitro-4-methylphenylsulfonylamino)-naphthalene
146 3,4-Bis(2-(1,2-cyclo(3-thioethyl)-4-chloro,5-imidazoylsulfonylamino)-naphthalene
147 2,3-Bis(4-methylsulfonophenylsulfonylamino)-naphthalene
148 1,2-Bis(4-fluorophenylsulfonylamino)-4-nitrobenzene
149 3,4-Bis(4-fluorophenylsulfonylamino)-benzoic acid methyl ester
150 3,4-Bis(4-trifluoromethylphenylsulfonylamino)-benzoic acid methyl ester

151	3,4-Bis(2-chloro-5-thienylsulfonylamino)-benzoic acid methyl ester
152	3,4-Bis(2-methoxy,2-chlorophenylsulfonylamino)-benzoic acid methyl ester
153	3,4-Bis(4-methyl,2-nitrophenylsulfonylamino)-benzoic acid methyl ester
154	1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene
155	1,2-Bis(2-thienylsulfonylamino)-4-fluorobenzene
156	1,2-Bis(3,4-dichlorophenylsulfonylamino)-4-fluorobenzene
157	1,2-Bis(2-methyl-5-nitrophenylsulfonylamino)-4-fluorobenzene
158	1,2-Bis(phenylsulfonylamino)-4,5-difluorobenzene
159	1,2-Bis(benzylsulfonylamino)-4,5-diflurobenzene
160	3,4-Bis(2,4-dichlorophenylsulfonylamino)-benzoic acid ethyl ester
161	3,4-Bis(2-chloro-5-thienylsulfonylamino)-benzoic acid ethyl ester
162	3,4-Bis(2-methyl-5-nitrophenylsulfonylamino)-benzoic acid ethyl ester
163	3,4-Bis(2,6-difluorophenylsulfonylamino)-benzoic acid ethyl ester
164	1,2-Bis(2-methyl-5-nitrophenylsulfonylamino)-4-methoxybenzene
165	1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-4-methoxybenzene
166	1,2-Bis(benzylsulfonylamino)-benzene
167	1,2-Bis(3,4-dichlorophenylsulfonylamino)-benzene
168	1,2-Bis(2-chloro-5-thienylsulfonylamino)-benzene
169	1,2-Bis(2-methyl-5-nitrophenylsulfonylamino)-benzene
170	1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-benzene
171	1,2-Bis(4-isopropylphenylsulfonylamino)-4-nitrobenzene
172	1,2-Bis(2-thienylsulfonylamino)-4,5-dimethylbenzene
173	1,2-Bis(3,4-dichlorophenylsulfonylamino)-4,5-dimethylbenzene
174	1,2-Bis(2-chloro-5-thienylsulfonylamino)-4,5-dimethylbenzene
175	1,2-Bis(2-methyl-5-nitrophenylsulfonylamino)-4,5-dimethylbenzene
176	1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-4,5-dimethylbenzene
177	1,2-Bis(4-methylsulfonophenylsulfonylamino)-4,5-dimethylbenzene
178	1,2-Bis(4-methylphenylsulfonylamino)-4-cyanobenzene
179	1,2-Bis(phenylsulfonylamino)-4-chlorobenzene
180	1,2-Bis(4-fluorophenylsulfonylamino)-4-chlorobenzene
181	1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene
182	1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4-chlorobenzene
183	1,2-Bis(2-thienylsulfonylamino)-4-chlorobenzene
184	1,2-Bis(3,4-dichlorophenylsulfonylamino)-4-chlorobenzene
185	1,2-Bis(4-isopropylphenylsulfonylamino)-4-chlorobenzene
186	1,2-Bis(2,4-difluorophenylsulfonylamino)-4-chlorobenzene
187	3,4-Bis(4-chloro-2-methoxyphenylsulfonylamino)-benzoic acid ethyl ester
188	1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4-chlorobenzene
189	1,2-Bis(2-chloro-5-thienylsulfonylamino)-4-chlorobenzene
190	1,2-Bis(2-methyl-5-nitrophenylsulfonylamino)-4-chlorobenzene
191	1,2-Bis(2-methyl-3-chlorophenylsulfonylamino)-4-chlorobenzene
192	1,2-Bis(4-cyanophenylsulfonylamino)-4-chlorobenzene
193	1,2-Bis(3,5-dimethyl-4-oxazoylsulfonylamino)-4-chlorobenzene
194	1,2-Bis(2,6-difluorophenylsulfonylamino)-4-chlorobenzene
195	1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-4-chlorobenzene
196	3,4-Bis(2,4-difluorophenylsulfonylamino)-benzoic acid methyl ester

197	3,4-Bis(2-methyl,5-nitrophenylsulfonylamino)- benzoic acid methyl ester
198	3,4-Bis(2-methyl,3-chlorophenylsulfonylamino)- benzoic acid methyl ester
199	3,4-Bis(2,6difluorophenylsulfonylamino)- benzoic acid methyl ester
200	1,2-Bis(2-chloro-5-thienylsulfonylamino)-4-fluorobenzene
201	1,2-Bis(2-methyl-3-chlorophenylsulfonylamino)-4-fluorobenzene
202	1,2-Bis(2-methoxy-5-chlorophenylsulfonylamino)-4-fluorobenzene
203	1,2-Bis(2-methyl-3-chlorophenylsulfonylamino)-3,4,5,6-tetramethylbenzene
204	3,4-Bis(2-thienylsulfonylamino)-benzoic acid ethyl ester
205	3,4-Bis(3-chloro-2-methylphenylsulfonylamino)-benzoic acid ethyl ester
206	1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-benzene
207	3,4-Bis(3-trifluoromethylphenylsulfonylamino)-benzoic acid methyl ester
208	1,2-Bis(2-(1,2-cyclo(3-thioethyl)-4-chloro-5-imidazoylsulfonylamino)-4-fluorobenzene
209	1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4,5-difluorobenzene
210	1,2-Bis(3-chloro-2-methylphenylsulfonylamino)-4,5-difluorobenzene
211	1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-4,5-difluorobenzene
212	1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-chloro-5-methylbenzene
213	2,3-Bis(2-thienylsulfonylamino) naphthalene
214	1,2-Bis(4-trifluoromethylphenylsulfonylamino)-4-chlorobenzene
215	1,2-Bis(4-fluorophenylsulfonylamino)-4,5-difluorobenzene
216	1,2-Bis(4-methylsulfonophenylsulfonylamino)-3,4,5,6-tetramethylbenzene
217	1,2-Bis(4-isopropylphenylsulfonylamino)-4-fluorobenzene
218	1,2-Bis(4-cyanophenylsulfonylamino)-4-fluorobenzene
219	1,2-Bis(4-methylphenylsulfonylamino)-4-cyanobenzene
220	3,4-Bis(8-quinolylsulfonylamino)-benzoic acid ethyl ester
221	1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4-fluorobenzene
222	1,2-Bis(phenylsulfonylamino)-4-fluorobenzene
223	3,4-Bis(3,5-dimethyl-4-oxazoylsulfonylamino)-benzoic acid methyl ester
224	3,4-Bis(4-isopropylphenylsulfonylamino)-benzoic acid methyl ester
225	1,2-Bis(4-methylphenylsulfonylamino)-4-chlorobenzene
226	3,4-Bis(3,5-dimethyl-4-oxazoylsulfonylamino)-4,5-difluorobenzoate
227	1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4-methoxybenzene
228	1,2-Bis(2-(1,2-cyclo(3-thioethyl)-4-chloro,5-imidazoylsulfonylamino)-4-methoxybenzene
229	1,2-Bis(phenylsulfonylamino)-4-cyanobenzene
230	1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-cyanobenzene
231	1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4-cyanobenzene
232	1,2-Bis(2-thienylsulfonylamino)-4-cyanobenzene
233	1,2-Bis(4-isopropylphenylsulfonylamino)-4-cyanobenzene
234	1,2-Bis(2,4-difluorophenylsulfonylamino)-4-cyanobenzene
235	1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4-cyanobenzene
236	1,2-Bis(3-chloro-2-methylphenylsulfonylamino)-4-cyanobenzene
237	1,2-Bis(2,6-difluorophenylsulfonylamino)-4-cyanobenzene
238	1,2-Bis(2-(3-oxazoyl)-5-thienylsulfonylamino)-4,5-difluorobenzene
239	1,2-Bis(4-trifluoromethoxyphenylsulfonylamino)-4-chloro-5-methylbenzene
240	1,2-Bis(benzylsulfonylamino)-4-chloro-5-methylbenzene
241	1,2-Bis(2-thienylsulfonylamino)-4-chloro-5-methylbenzene
242	1,2-Bis(3,4-dichlorophenylsulfonylamino)-4-chloro-5-methylbenzene

243	1,2-Bis(4-trifluoromethylphenylsulfonylamino)-4-chloro-5-methylbenzene
244	1,2-Bis(2,4-difluorophenylsulfonylamino)-4-chloro-5-methylbenzene
245	1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4-chloro-5-methylbenzene
246	3,4-Bis(2,4-dimethyl-5-oxa-3-thiazoylsulfonylamino)-4-chloro-5-methylbenzene
247	1,2-Bis(2-aza-4,5-benzothiazoylsulfonylamino)-4-chloro-5-methylbenzene
248	1,2-Bis(2-(5-oxa-2-thiazoyl)-5-thienylsulfonylamino)-4-chloro-5-methylbenzene
249	1,2-Bis(2,4-difluorophenylsulfonylamino)-4-chloro-5-methylbenzene
250	1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-4-chloro-5-methylbenzene
251	1,2-Bis(4-methyl-3-nitrophenylsulfonylamino)-4-cyanobenzene
252	1,2-Bis(phenylsulfonylamino)-4-chloro-5-methylbenzene
253	2,3-Bis(2,4-dichlorophenylsulfonylamino)naphthalene
254	1,2-Bis(2,4-dichlorophenylsulfonylamino)-benzene
255	1,2-Bis(2-(2-methyl-4-thiazoyl)-5-thienylsulfonylamino)-benzene
256	1,2-Bis(2-(2-methyl-4-thiazoyl)-5-thienylsulfonylamino)-4,5-dimethylbenzene

The above compounds were analysed by liquid chromatography, in conjunction with a mass spectrometer as detector. The equipment used was a Waters 2700 Sample Manager, with Waters 2690 Alliance Solvent Delivery System and Waters 996 Photodiode Array Detector. The mass spectrometer used was a Micromass Platform LCZ Mass Spectrometer running Micromass MassLynx Software, v3.2 build 004. Chromatography was carried out on a Waters Symmetry 3.5μm C18 50x2.0mm (WAT200650) column with a gradient elution from 5% 10mM formic acid in acetonitrile and 95% 10mM formic acid in water to 95% 10mM formic acid in acetonitrile and 5% 10mM formic acid in water over 3 minutes at 0.5ml/minute flow rate. UV detection was at 200-300nm and mass spectra were collected by positive and negative electrospray. All reaction products showed the desired compound with satisfactory purity.

Example 257

3,4-Bis(4-methylphenylsulfonylamino)-benzoic acid

3,4-Bis(4-methylphenylsulfonylamino)-benzoic acid methyl ester (Example 8, 3.5g, 7.38 x 10^{-4}mol) was stirred in 1N sodium hydroxide solution (250 mL) at 60 °C for 5 hr. After this time the solution was cooled and the precipitate filtered, washed with water and recrystallised from acetic acid and water to yield 2.0g, 59 % of the title compound.

Example 258

1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-(3-methyloxadiazole-5-yl) benzene

N-hydroxy-acetamidine (0.028g,0.39mmol) in THF (dry,15ml) was added to a stirred solution of dry THF (5ml) containing sodium hydride (0.015g, 0.39mmol). The mixture was heated to 60ºC under nitrogen. A solution of 3,4-Bis(3-trifluoromethylphenylsulfonylamino)-benzoic acid methyl ester (Example 207, 76mg, 0.13mM) in dry THF (15ml) was added dropwise over 15mins. The reaction was left to reflux overnight. Methanol (5ml) then Water (5ml) were added sequentially and the mixture concentrated to dryness. The crude micture was subjected to column chromatography on silica with methanol / dichloromethane to yield the product (21mg, 27%)

Example 259

3,4-Bis(4-methylphenylsulfonylamino)-*N*-phenyl-benzamide

3,4-Bis(4-methylphenylsulfonylamino)-benzoic acid (Example 257, 0.092 g, 0.2 mmol), aniline (0.0186 g, 0.2 mmol), *N*, *N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (0.172 g, 0.6 mmol, loading 3.5 mmol/g) and *O*-(7-azabenzotriazol-1-yl)-*N*, *N*, *N*, *N*-tetramethyluronium hexafluorophosphate (HATU) (0.076 g, 0.2 mmol) was stirred under nitrogen in anhydrous acetonitrile (8 mL) and heated to 50 °C for 40 hr. After this time the reaction mixture was cooled to room temperature. A sequestration enabling reagent - tetrafluorophthalic anhydride (0.132 g, 0.6 mmol) was then added and the reaction mixture was stirred under nitrogen for 18 hours. Macroporous triethylammonium methylpolystyrene carbonate resin (MP-carbonate, 0.630 g, 2.0 mM, loading 3.18 mM/g) was then added and the reaction mixture was stirred under nitrogen for a further 48 hours. The reaction mixture was then filtered through a filter syringe into a vial and the precipitate washed with methanol. The combined solvent was

removed on a vacuum concentrator to yield 0.051 g, 48 %. The product was analysed by LC-MS and had 85.0 % purity.

Examples 260 and 261.

The compounds set out below were prepared in the same way as Example 259, using appropriate starting materials.

Example	Compound
260	3,4-Bis(4-methylphenylsulfonylamino)-*N*-(4-fluoromethoxyphenyl) benzamide
261	3,4-Bis(4-methylphenylsulfonylamino)-*N*-(3,5-dimethoxyphenyl) benzamide

Example 262

3-(2-Phenyl-ethenesulfonylamino)-4-(3-trifluoromethylbenzenesulfonylamino)-benzoic acid ethyl ester

4-(3-trifluoromethylsulfonylamino)-3-nitro-benzoic acid ethyl ester (prepared as per Example 22 from appropriate starting materials; 1.00g, 2.66mmol) was dissolved in ethanol (50ml). This solution was stirred and palladium on carbon (5%) added slowly followed by ethanol to wash vessel sides and then an excess of hydrazine hydrate (2ml). This solution was refluxed for 18 hr filtered and evacuated to dryness. The product was then purified on silica using methanol/chloroform as the eluent to yield 3-amino-4-(3-trifluoromethylbenzenesulfonylamino)-benzoic acid ethyl ester as a dry white solid (0.81g, 89%). This material was then reacted with 2-phenylethenesulfonyl chloride as per example 22 to provide the title product.

Examples 263 to 271

The compounds set out below were prepared in the same way as Example 262, using appropriate starting materials.

Example	Compound
263	1-(4-methoxyphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene
264	1-(3-chlorophenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene
265	1-(2-chlorophenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene
266	1-(3-methylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene
267	1-(4-methylamidomethylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene
268	1-(2-(phenylamidomethyl)-5-thienylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene
269	1-(4-(2-chloro-5-thiazoylmethoxyphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene
270	3-(2,5-dichloro-3-thienylsulfonylamino),4-(3-trifluoromethylsulfonylamino)-methylbenzoate
271	3-(4-methylphenylsulfonylamino),4-(3-trifluoromethylphenylsulfonylamino)-methylbenzoate

Example 272

1-(4-methylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene.

1-Nitro-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene (prepared as per example 22 using appropriate starting materials; 0.13g, 0.32mmol) was stirred in dimethylformamide (5ml) containing tin (II) chloride (0.28g, 1.25mmol). The reaction was left to stir overnight at room temperature under nitrogen. The mixture was diluted with water (15ml) and the pH adjusted to 7 with 1M sodium hydroxide solution. The aqueous solution was extracted with chloroform and the chloroform removed under vacuum to yield an orange oil. This was purified by flash chromatography on silica using methanol/chloroform to yield 1-amino-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene (0.07g, 58%). This material was then reacted with 4-methylphenylsulfonyl chloride in the same way as Example 22 to provide the title compound.

Examples 273 to 285

The compounds set out below were prepared in the same way as Example 272, using appropriate starting materials.

Example	Compound
273	1-(4-methylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene
274	1-(3-trifluoromethylsulfonylamino)-2-(2-phenylethenylsulfonylamino)-4-fluorobenzene
275	1-(3-trifluoromethylsulfonylamino)-2-(2-phenylethenylsulfonylamino)-benzene
276	1-(3-trifluoromethylsulfonylamino)-2-(benzylsulfonylamino)-4-fluorobenzene
277	1-(2,5-dichloro-3-thienylsulfonylamino)-2-(3-trifluoromethylsulfonylamino)-benzene
278	1-(2-(phenylamidomethyl)-5-thienylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-benzene
279	1-(2-(phenylamidomethyl)-5-thienylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene
280	1-(4-(2-chloro-5-thiazoylmethoxyphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-benzene
281	1-(4-(2-chloro-5-thiazoylmethoxyphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene
282	1-(2-chlorophenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-benzene
283	1-(2-chlorophenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene
284	1-(2-methylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-benzene
285	1-(3-methylphenylsulfonylamino)-2-(3-trifluoromethylphenylsulfonylamino)-4-fluorobenzene

Example 286

Analytical Data for compounds representative of Examples 1 to 285

Example	NMR Data	Mass Spectrum, technique	Micro Analysis Calc.d (found)
1	δ_H(CD_3COCD_3, 400MHz) 6.95 (2H, dd, *J* 8,2Hz); 7.85 (2H, t, *J* 8Hz,); 8.10 (2H, dd, *J* 8,2 Hz); 8.45 (4H, m),	478 (M^+) EI	
25	δ_H(CD_3COCD_3, 400MHz) 2.35 (6H, s); 6.65 (2H, bs); 7.10 (2H, s); 7.20 (4H, d, *J* 8Hz); 7.50 (4H, d, *J* 8Hz),	574 (M^+) EI	
11	δ_H(CD_3COCD_3, 400MHz) 6.96 (2H, m);	546 (M^+), EI	

	7.05 (4H, AB d, *J* 8.1Hz); 7.07 (2H, m); 7.58 (4H, AB d, *J* 8.1Hz).		
12	$\delta_H(CD_3COCD_3$, 400MHz) 1.26 (18H, s); 6.73, 4H, m); 7.36 (4H, AB d, *J* 8.9Hz); 7.57 (4H, AB d, *J* 8.9Hz).	500 (M^+), EI	
15	$\delta_H(CD_3COCD_3$, 400MHz) 2.35 (6H, s); 3.53 (4H, s); 6.51 (2H, s); 7.31 (4H, AB d, *J* 8.0Hz); 7.58 (4H, AB d, *J* 8.0Hz).	452 (M^+), EI	
16	$\delta_H(CD_3COCD_3)$ 2.33 (6H, s); 7.28 (4H, AB d, *J* 8.3Hz); 7.40 (2H, m); 7.53 (2H, s); 7.64 (4H, AB d, *J* 8.3Hz); 7.68 (2H, m).		
17	$\delta_H(CD_3COCD_3$ 400MHz) 2.39 (6H, s); 6.99 (2H, t, J_{F-H} 9.8Hz); 7.35 (4H, AB d, *J* 7.9Hz); 7.60 (4H, AB d, *J* 7.9Hz).		
59	$\delta_H(CDCl_3$, 300MHz) 6.95 (2H, m); 7.05 (2H, m); 7.15 (2H, bs); 7.25 (4H, m); 7.75 (4H, m)		C: 43.17 (43.00), H: 2.54 (2.19), N: 5.03 (4.91)
140	$\delta_H(CD_3COCD_3$, 400MHz) 2.75 (6H, s); 7.2-7.3 (2H, t, *J* 8Hz); 7.4-7.5 (2H, m); 7.55 (2H, s); 7.6-7.7 (4H, m); 7.75-7.80 (2H, d, *J* 8 Hz); 9.0 (2H, bs)	534 $(M-H)^-$, FAB	C: 53.83 (54.19) H: 3.96 (3.69) N: 5.23 (5.08)
181	$\delta_H(CD_3COCD_3$, 400Hz) 6.75 (1H, d, *J* 8.6Hz); 6.90 (1H, d, *J* 2.3Hz); 6.98 (1H, dd, *J* 8.6, 2.3Hz); 7.65 (2H, t, *J* 7.9Hz); 7.77-7.88 (6H, m)	559 $(M-H)^-$, FAB	C: 42.98 (43.05) H: 2.34 (2.06 N: 5.01 (4.86

182	$\delta_H(CD_3COCD_3$, 400MHz) 6.81 (1H, d, *J* 9Hz); 6.92 (1H, d, *J* 2.4Hz); 6.97 (1H, dd, *J* 9, 2.4Hz); 7.43 (4H, m); 7.68 (4H, m)	590 $(M-H)^-$, ES –ve,	C: 40.61 (40.65) H: 2.22 (1.93) N: 4.74 (4.56)
188	$\delta_H(CDCl_3$, 300MHz) 7.0-7.6 (5H, m)	571 $(M-H)^-$, Es –ve	C: 29.36 (29.19) H: 1.23 (0.97) N: 4.89 (4.49)
189	$\delta_H(CD_3COCD_3$, 400MHz) 7.6-8.1 (7H, m); 9.4 (2H, bs)	502 $(M-H)^-$, Es –ve	C: 33.57 (33.37) H: 1.62 (1.80) N: 5.51 (5.56)
200	$\delta_H(CD_3OD$, 300MHz) 6.85-6.95 (1H, m); 6.95-7.0 (1H, m); 7.0-7.05 (2H, m); 7.08 (1H, dd, *J* 10, 3Hz); 7.25 (1H, d, *J* 3Hz); 7.38 (1H, d, *J* 3Hz)	485 $(M-H)^-$, Es –ve	C: 34.50 (34.71) H: 1.86 (1.61) N: 5.75 (5.67)
201	$\delta_H(CDCl_3$, 300MHz) 2.55 (3H, s); 2.63 (3H, s); 6.43-6.47 (2H, m); 6.74 (1H, dd, *J* 10, 3Hz); 7.11-7.44 (2H, m); 7.45-7.6 (3H, m); 7.71 (1H, d, *J* 10Hz)	503 $(M^+)^-$, FAB	C: 47.72 (47.52) H: 3.40 (3.19) N: 5.56 (5.45)
242	$\delta_H(CD_3COCD_3$, 400MHz) 2.2 (3H, s); 7.1 (2H, d, *J* 10Hz); 7.6-7.7 (2H, m); 7.75-7.80 (2H, m); 7.85 (2H, m); 8.6-8.7 (2H, bs)	573 $(M-H)^-$, Es –ve	C: 39.71 (39.90) H: 2.28 (2.11) N: 4.87 (4.72)
268	$\delta_H(CDCl_3$, 400MHz) 4.8 (2H, d, *J* 5Hz);	628 $(M-H)^-$, Es	C: 47.66 (47.68)

	6.3 (1H, d, *J* 9Hz); 6.8 (1H, dd, *J* 8, 4Hz); 6.9 (1H, d, *J* 4Hz); 7.2 (1H, m); 7.3 (1H, d, *J* 6Hz); 7.35-7.45 (3H, m); 7.5-7.6 (2H, m); 7.65-7.8 (4H, m)	–ve	H: 3.04 (3.04) N: 6.67 (6.57)
269	$\delta_H(CD_3COCD_3$, 400MHz) 5.2 (2H, s); 6.85 (1H, d, *J* 8Hz); 6.9-7.0 (3H, m); 7.3 (1H, m); 7.5 (1H, s); 7.6 (1H, t, *J* 10Hz); 7.6-7.7 (2H, m); 7.8 (1H, d, *J* 8Hz); 7.85 (1H, d, J 8Hz); 7.9 (1H, s); 8.5 (2H, bs)	636 $(M-H)^-$, Es –ve	C: 43.27 (43.84) H: 2.53 (2.47) N: 6.58 (6.64)
277	$\delta_H(CDCl_3$, 300MHz) 6.92 (1H, s); 7.03-7.21 (4H, m); 7.65 (1H, t, *J* 9Hz); 7.86 (1H, d, *J* 9Hz); 8.0 (2H, s)		C: 38.43 (38.36) H: 2.09 (1.86) N: 5.27 (5.15)

Example 287

Inhibition of purified dehydroquinate synthetase (AroB) measured in 96-well plates at single concentrations (50μM). Briefly, a three-enzyme linked assay employing dehydroquinate synthase (AroB), dehydroquinase (Type I) and dehydroshikimate dehydratase (DHSD) was constructed. In the presence of this enzyme mixture the substrate, 3-Deoxy-D-arabino heptulosonic acid-7-phosphate (DAHP), is converted into protocatechuic acid, which can be quantified using a spectrophotometric plate reader set at 290nm. A second incubation, after addition of 0.1% ferric chloride, allows measurement of a protocatechuic acid-iron complex at 570nm. In the absence of inhibitors, the DAHP concentration in the assay is adjusted to give an absorbance of 1 unit at 290nm after the initial stage of the assay. Compounds were tested at 50μm for their ability to reduce the absorbance at 290nm and 570nm at the respective stages of the assay, representing reduced conversion of

DAHP to protocatechuic acid by the enzyme mixture. The assay medium also contained buffer (morpholino propanesulfonic acid at pH 7.0), cobalt chloride (40μM final conc.n), zinc sulfate (40μM) and magnesium sulfate (2.5mM). NAD was added as co-factor at 20μM.

A follow-up dehydroquinase assay was used to confirm that active compounds were inhibiting dehydroquinate synthase. This assay was carried out similarly to above, but employing dehydroquinate as the substrate and omitting dehydroquinate synthase from the assay medium. None of the tested compounds showed any activity in the modified assay, hence all actives were shown to be inhibiting dehydroquinate synthase only.

Example	Reduction in absorbance at 290nm	Reduction in absorbance at 570nm
1	50	40
25	79	84
2	88	99
3	51	68
22	76	100
5	88	100
23	21	44
9	50	61
7	87	100
8	10	15
11	89	96
26	18	36
14	90	98
16	81	100
17	88	99
18	77	92
20	79	91
21	75	88
59	73	76
60	29	33
61	29	33
62	30	30
63	21	34
64	22	24
66	20	24
67	36	41
68	18	28

70	18	17
71	32	36
72	35	31
73	12	38
74	17	34
75	27	88
76	39	76
77	41	92
78	9	23
79	23	50
80	8	20
81	5	18
82	5	21
84	7	18
85	8	22
86	5	17
87	8	19
88	48	93
89	3	20
90	3	15
91	8	23
92	7	19
93	5	24
94	8	17
95	10	26
96	6	22
97	8	13
98	10	17
99	12	7
100	11	14
101	44	82
102	48	95
103	9	26
104	11	26
105	84	98
106	68	97
107	80	94
110	82	94
112	55	76
113	5	62
115	39	58
118	21	35
119	90	95
121	90	103
124	40	90
125	54	87

126	59	66
27	100	100
28	68	97
29	5	62
30	70	97
31	69	99
32	59	66
33	82	100
34	25	88
35	80	100
36	49	61
37	68	88
38	71	101
39	98	103
40	83	100
41	42	95
42	0	97
43	68	97
45	70	93
46	80	80
47	60	60
48	40	40
49	40	40
50	50	50
52	20	50
53	50	50
54	80	84
55	100	100
56	100	100
57		79
58	50	5.00E+01
128	40	90
129	20	30
131	51	65
132	83	94
133	79	96
134	73	95
135	0	20
136	85	96
137	50	70
138	84	98
139	47	68
140	85	94
141	45	68
142	66	75
143	59	80

144	76	88
145	86	96
146	73	85
148	20	33
149	84	101
150		89
151	80	94
153	73	86
154	86	94
156	72	91
157	2	36
158	24	39
160		23
161	82	94
162	29	60
163	4	32
165	80	93
167	68	70
168	55	76
169		37
171	69	84
173	10	33
174	39	58
176	31	45
178		34
179	49	70
180	8	43
181	88	100
182	85	98
183	21	35
184	89	103
185	84	94
186	80	98
187	23	51
188	88	101
189	90	95
190	62	89
191	93	103
192	32	55
193	20	32
194	18	31
195	83	35
196		82
197		79
198	79	96
199		32

200	90	103
201	92	96
202	23	51
205	72	99
206	64	92
207	20	100
208	39	50
209	63	62
210	72	64
211	63	84
212	68	99
213	34	42
214	43	50
215	49	77
216	10	39
217	50	60
218		40
219	90	75
220		70
221	80	80
222		37
223		40
224	50	80
225	80	74
226	44	44
227	70	70
228	40	40
229	50	50
230	30	30
231	80	75
232	20	50
233	90	90
234		50
235	80	50
236	90	90
237	50	50
238	90	85
239	20	56
240	98	100
241	50	50
242	99	98
243	80	75
244	85	90
245	100	100
246	80	80
247	70	60

248	90	95
249	50	65
250	90	85
251	89	90
252	50	50
253	80	70
254		40
255	30	50
256	65	47
258	40	89
259	34	73
260	64	89
261	59	73
262		8.00E+01
263	60	60
264	95	98
265	100	100
266	80	85
267	50	50
268	100	100
269	95	97
270		47
271		47
272	71	80
273	53	87
274	37	64
275	68	9.20E+01
276	73	88
277		74
278		68
279		45
280		73
282		63
283		74
284		38

Example 288

Inhibition of purified dehydroquinate synthetase (AroB) was measured in 96-well plates using the method set out in Example 287. Experiments were repeated at different concentrations to allow IC_{50} values to be calculated. The IC_{50} values were calculated at 290 nm.

Example	IC_{50} (μM)
16	5
18	7
25	8
2	10
21	12
128	12
102	15
8	15
17	20
59	20
129	20
77	20
88	20
22	20
5	20
7	30
3	60
20	30
76	30
75	40
101	50
105	10
106	15
112	10
103	11
105	11
127	11
130	5
131	90
132	10
133	10
134	10
135	100+
136	7
137	50
138	10
139	32
140	12
141	13
142	15
143	20
144	30
145	15
146	10
148	25
149	60
151	25
153	30
154	8
156	5
158	40
160	50
161	10
162	20
163	60
165	17
167	6
168	10
171	7
174	11
176	11
179	94
180	62
181	3
182	5
185	18
186	24
188	11
189	3
190	44
191	18
192	50
195	9
196	30
197	40
198	7
199	64
200	6
201	6
205	6
206	8
207	20
208	>100
209	80
210	60
211	25
212	15
213	80
214	8
215	15
216	>100
217	12
219	7
220	100+
221	5
224	12
225	18

227	42	**268**	7
228	61	**269**	6
229	105	**27**	6
230	3	**270**	86
231	20	**271**	82
232	120	**272**	28
233	10	**273**	26
234	300+	**274**	>300
235	42	**275**	54
236	4	**276**	36
237	50	**28**	15
238	13	**29**	11
239	80	**30**	12
240	6	**31**	20
241	18	**32**	60
242	38	**33**	15
243	14	**34**	50
244	13	**35**	10
245	7	**36**	50
246	18	**37**	100+
247	20	**38**	100+
248	6	**39**	8
249	28	**40**	10
250	16	**41**	60
251	7	**42**	30
252	50	**43**	8
253	30	**45**	10
254	>100	**46**	7
255	40	**47**	25
256	>100	**48**	60
258	10	**49**	60
260	58	**50**	6.5
262	56	**52**	56
263	30	**53**	5.5
264	10	**54**	40
265	8	**55**	10
266	20	**56**	10
267	45	**58**	16

Example 289

Inhibition of purified *M. tuberculosis* Type II dehydroquinase (AroQ) was measured in 96-well plates at single concentrations (50μM). Briefly, a two-enzyme linked assay employing AroQ and dehydroshikimate dehydratase (DHSD) was constructed. In the presence of this enzyme mixture the substrate, quinate, is converted into protocatechuic acid, which can be quantified (using a spectrophotometric plate reader set at 570nm) after 2 minutes incubation with 0.1% ferric chloride. Compounds were tested at 50μM for their ability to reduce the

absorbance at 570nm, representing reduced conversion of quinate to protocatechuic acid by the enzyme mixture. The assay medium also contained buffer (morpholino propanesulfonic acid at pH 7.0), cobalt chloride (40μM final conc.n), zinc sulfate (40μM) and magnesium sulfate (2.5mM).

A follow-up assay was used to confirm that active compounds were inhibiting the dehydroquinase. Briefly, compounds were incubated in the presence of AroQ in the usual buffer mix and their ability to reduce conversion of quinate to dehydroshikimic acid measured in a spectrophotometer at 240nm. All of the tested compounds showed activity in the modified assay, and are thus shown to be inhibitors of the dehydroquinase.

Example	Reduction in absorbance at 570nm
25	40
5	40
14	65
18	50
21	60
76	74
77	80
84	20
102	75
105	76
106	100
107	63
108	41
109	18
110	67
111	24
112	76
113	100
114	34
115	64
116	25
117	49
118	35
119	76
120	27
121	80

Example	Reduction in absorbance at 570nm
122	22
123	44
126	72
27	50
28	100
29	100
30	100
31	49
32	72
33	100
34	46
35	40
36	60
37	50
38	99
39	63
40	50
44	100
45	82
46	100
47	60
49	40
51	80
52	62
58	50
131	48
132	42

133	78	**173**	36
134	53	**174**	64
135	100	**175**	43
136	56	**176**	44
137	59	**177**	37
138	76	**178**	32
139	53	**179**	32
140	54	**180**	36
141	47	**181**	60
142	33	**182**	44
143	53	**183**	35
144	56	**184**	100
145	84	**185**	33
146	54	**186**	43
147	51	**187**	39
149	100	**188**	85
150	60	**189**	76
151	63	**190**	47
152	47	**191**	43
153	44	**195**	89
154	67	**196**	35
155	41	**197**	48
156	100	**198**	52
157	47	**199**	46
158	31	**200**	80
159	40	**201**	50
159	96	**203**	31
160	41	**204**	44
161	67	**205**	79
162	58	**227**	72
163	45	**231**	50
164	44	**232**	50
165	64	**233**	90
166	31	**236**	95
167	88	**238**	40
168	76	**242**	50
169	37	**248**	50
170	50	**249**	60
171	100	**251**	80
172	34	**257**	33

Example 290

Inhibition of purified mycobacterium tuberculosis type II dehydroquinase (AroQ) was measured in 96 well plates using the method set out in

Example 289. Experiments were repeated at different concentrations to allow IC_{50} values to be calculated. The IC_{50} values were calculated using results at 570nm.

Example	IC_{50} (μm)	Example	IC_{50}(μm)
105	10	**140**	18
106	2	**143**	45
107	50	**144**	35
108	60	**145**	25
112	20	**146**	30
113	20	**149**	18
115	45	**151**	50
119	15	**154**	25
121	6	**155**	60
126	25	**156**	3
27	50	**159**	66
28	2	**165**	20
29	20	**167**	48
30	10	**171**	18
31	100	**176**	88
32	25	**181**	15
33	27	**184**	4
35	57	**186**	5
36	50	**188**	5
37	40	**189**	18
38	2	**191**	90
39	20	**195**	35
40	40	**198**	90
44	20	**200**	6
45	100	**205**	15
46	18	**227**	30
47	25	**231**	30
49	60	**232**	65
51	15	**233**	18
52	14	**236**	20
58	5	**238**	40
131	60	**242**	50
133	20	**248**	60
135	6	**249**	28
136	60	**251**	50
138	10	**257**	7

Example 291

Antibacterial activity of compounds against *Staphyloccocus aureus.*

The method set out below was used to determine the Minimum Inhibitory Concentration (MIC) of compounds against methicillin sensitive and resistant strains of *Staphylococcus aureus.* It is a modification of the method used in clinical laboratories to determine anti-microbial susceptibility (NCCLS M7-A4 Methods for dilution anti-microbial susceptibility tests for bacteria that grow aerobically 4th edition).

The broth media used for the assay was 9 parts M9 Minimal Salts to 1 part Luria (Lennox) Media (9:1 M9:LB).

M9 Minimal Salts		Luria (Lennox) Media
NaCl	1.00 g/l	NaCl 5.00 g/l
Na_2HPO_4	6.78 g/l	Yeast extract 5.00 g/l
KH_2PO_4	3.00 g/l	Enzymatic casein digest 10.00 g/l
NH_4Cl	1.00 g/l	

For agar plates this media was solidified by addition of 1.5% (w/v) Noble Agar.

3ml 9:1 M9:LB broth was inoculated with a single colony from a fresh culture of methicillin sensitive or methicillin resistant strain of *Staphylococcus aureus* grown on 9:1 M9:LB agar. This was incubated at 37°C with shaking (~250rpm) for 4-5 hrs. Optical density of the broth was measured at 600nm and the culture diluted to give an A_{600} of ~0.1 in sterile 0.85% saline. Miles and Misra's were carried out on the diluted inoculum as follows:

a) 90µl of sterile 0.85% saline was added to the remaining wells of the microtitre plate (rows B to H) ;

b) 10µl of culture was taken from row A to row B and mixed well. The serial dilution was continued down the plate, changing tips with each transfer;

c) in triplicate, 5µl volumes of each dilution were transferred to the surface of a dry agar plate. The plates were left for around 1hr to allow the drops of liquid to dry into the agar; and

d) the plates were incubated at 37°C overnight and the number of colonies at a dilution where there are between 10 & 50 discrete colonies per spot were counted. The appropriate calculation (see below) was then used.

200µl of 9:1 M9:LB Broth was added to the top row of wells in a sterile microtitre plate, to this 10µl of the compound of Example 25 in dimethyl sulphoxide (DMSO) was added to the wells in duplicate. To one of the duplicates 2µl of 10mg/ml Phenylalanine, 2µl of 10mg/ml Tryptophan, 40µl of 0.5mg/ml Tyrosine and 2µl of 5µg/ml p-Aminobenzoic acid were added. The wells were then inoculated with 5µl of the diluted bacterial culture (see above). The microtitre plates were incubated at 37°C with shaking (~150rpm) for 16-20 hrs and the A_{600} recorded, Miles and Misra's were then performed on the cultures (see above).

The criteria used for determining the >MIC= (bactericidal concentration) was the concentration at which a sub-cultured broth from the drug-treated batch shows no growth on media free of anti-microbial agent. The bacteriostatic concentration was calculated by testing the compound at a narrow range of molarities just above the MIC. A curve was then plotted of the total number of bacteria in the well of the microplate as a percentage of the number of bacteria that the wells were inoculated with.

The used calculations for the results were c.f.u./ml = (number of colonies X dilution factor) X 200. Number of bacteria in inoculum = c.f.u./ml / 200. Total number of bacteria in well = c.f.u./ml / 5

Activity against Smith Strain (Methicillin sensitive) *Staphyloccocus aureus*

Example	MIC (μM)	Example	MIC (μM)
1	1	**178**	100+
5	300	**181**	1.2
7	1	**182**	1
18	15	**184**	2.2
25	1	**185**	20
27	4	**186**	>30
28	30+	**188**	0.5
30	30+	**189**	2
32	30+	**191**	2.7
33	30+	**195**	30+
39	30+	**198**	30
43	10	**200**	30
46	>30	**201**	0.4
59	4.2	**205**	5
72	9	**206**	6
102	30	**212**	7.5
127	0.4	**215**	30+
132	14	**217**	30+
133	12	**219**	6.5
134	8	**221**	7
135	30+	**224**	30+
136	3	**225**	30+
137	100+	**230**	30
138	100+	**233**	25
139	30+	**236**	30
140	30	**238**	30
141	30+	**239**	3
142	100+	**240**	30+
143	30+	**241**	3
145	30+	**243**	3
146	30+	**244**	30
148	100+	**245**	2
149	30	**246**	30+
150	10	**247**	30+
151	100+	**248**	30+
153	100+	**249**	30+
154	8	**250**	30+
156	6	**251**	30+
161	30+	**258**	>30
162	30+	**260**	>30
165	30	**272**	>30
167	13	**273**	>30
171	3.4	**274**	>30
		275	>30
		276	1.5

Activity against Methicillin Resistant *Staphyloccocus aureus*

Example	Methicillin resistant *S. aureus* strain	MIC (μM)
25	MecA+ 10196/7	5
25	MecA+ 320/97	5
25	MecA+ 1789/97	5
25	MecA+ 4099/98	5
25	MecA+ 7623/98	5
25	MecA+ 8038/97	10
25	MecA+ 7449	20
25	MecA+ 2298	20
25	MecA+ 5033/98	20
25	MecA+ 1905/98	20
182	NCTC 12493	5
188	NCTC 12493	2
201	NCTC 12493	5

Example 292

Toxicity against the VERO cell line.

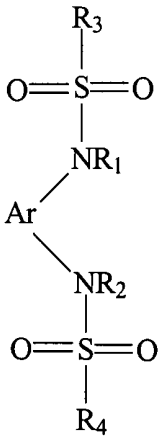
Cells are routinely cultured in Dulbecco's Modified Eagle Medium (DMEM), with L-Alanyl-L-Glutamine (Gibco 21885-025), containing 10% Foetal Bovine Serum (FBS) (Gibco 16000-044). The process followed comprises:

1. On day 1 100μl of cells ate seeded at 5 x 10^4 cell/ ml in a 96 well plate.
2. On day 2 having allowed cells to attach, compounds are diluted in growth medium (DMEM) to 2X final required concentration, from a 20mM stock made up in DMSO, and add 100μl per well. 0.5% DMSO made up in growth medium is added to the control wells.
3. Cells are incubated at 37ºC, 5% CO^2 for 72-96 hours.
4. Medium is removed by aspiration and cells are stained by adding 100μl methylene blue (0.5% in 50% EtOH) per well, and incubated at room temperature for 1 hour. The stain was then washed off under running water and left to air dry.
5. Cells can be examined for signs of changes in morphology.
6. Stain is released from the cells by addition of 100μl of solubilisation solution (1% N-lauryl sarcosine, Sigma L-5125, in distilled water), and gently shook for 1 hour. Plates are then read measuring the OD at 620nm. The percentage inhibition of cell growth was calculated relative to non-drug treated control wells.

Example	Toxicity MIC(μM)	Example	Toxicity MIC(μM)
1	30	**184**	64
18	70	**185**	32
20	45	**188**	65
21	60	**189**	40
27	28	**201**	22
28	>100	**219**	38
43	75	**221**	23
53	62	**224**	42
59	15	**225**	61
72	25	**233**	75
132	25	**237**	>100
133	40	**238**	100
134	23	**239**	16
136	>100	**240**	40
140	10	**241**	36
141	2	**243**	28
142	2	**244**	22
150	23	**245**	31
154	21	**246**	34
156	60	**247**	>100
167	35	**248**	100
171	85	**249**	>100
181	50	**250**	76
182	33	**252**	81

CLAIMS

1. Use of a bissulfonamide derivative of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inhibiting the biosynthesis of aromatic amino acids via the shikimate pathway,



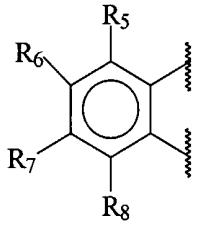
(I)

wherein:

- Ar is an aryl or heteroaryl group;
- R_1 and R_2 are the same or different and each represent hydrogen or alkyl or R_1 and R_2 together form a C_1-C_3 alkylene group, -CO- or -CS-; and
- R_3 and R_4 are the same or different and each represent -alkyl-aryl, -alkyl-heteroaryl, -alkenyl-aryl, -alkenyl-heteroaryl, -alkynyl-aryl -alkynyl-heteroaryl, aryl or heteroaryl.

2. Use according to claim 1 wherein R_3 and R_4 are the same or different and each represent an aryl or heteroaryl group.

3. Use according to claim 1 wherein Ar is a group Ar'



(Ar')

wherein R_5 to R_8 are the same or different and represent aryl, heteroaryl, heterocyclyl, cyano, nitro, halogen, alkyl, haloalkyl, alkoxy, alkylthio, haloalkoxy, hydroxy, -CO_2R wherein R is aryl, heteroaryl, hydrogen or alkyl, or -NR'R'' or -CONR'R'' wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together form an alkylenedioxy group or, together with the carbon atoms to which they are attached, form a phenyl moiety.

4. Use according to claim 3, wherein R_5 and R_8 are the same or different and represent hydrogen, halogen, alkyl, hydroxy, alkoxy or -NR'R'' wherein R' and R'' are the same or different and are hydrogen or alkyl and R_6 and R_7 are the same or different and represent hydrogen, aryl, heteroaryl, heterocyclyl, nitro, cyano, halogen, alkyl, haloalkyl, alkoxy, alkylthio, haloalkoxy, hydroxy, -CO_2R wherein R is aryl, heteroaryl, hydrogen or alkyl, or -NR'R'' or -CONR'R'' wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, or R_6 and R_7 together form an alkylenedioxy group or, together with the carbon atoms to which they are attached, form a phenyl moiety.

5. Use according to claim 4 wherein one of R_5 and R_8 is hydrogen, and the other is hydrogen, halogen or hydroxy and R_6 and R_7 represent hydrogen, aryl, heteroaryl, nitro, cyano, alkyl, alkoxy, haloalkyl, halogen, -CO_2H, -CO_2-alkyl or -CONR'R'' wherein R' and R'' are the same or different and are aryl,

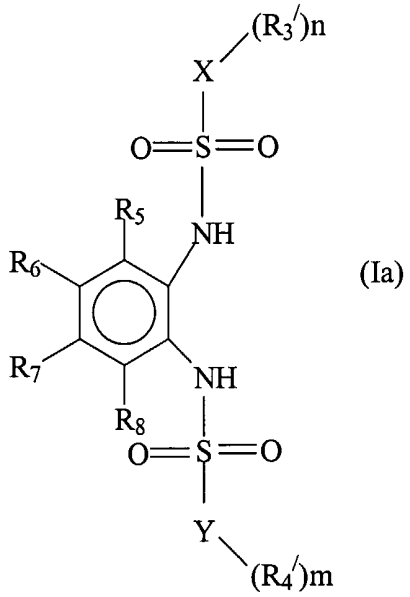
heteroaryl, hydrogen or alkyl, or R_6 and R_7 together form an alkylenedioxy group or a phenyl moiety.

6. Use according to any one of the preceding claims wherein R_1 and R_2 are the same or different and represent hydrogen or alkyl or R_1 and R_2 together form a C_1-C_3 alkylene group.

7. Use according to any one of the preceding claims wherein R_3 and/or R_4 is phenyl, naphthyl, pyridyl, furanyl, thienyl, imidazolyl, pyrazolidinyl, isoxazolyl, pyrrolyl, (1,2-cyclo(3-thioethyl)-imidazolyl, benzothienyl, indolyl or quinolinyl.

8. Use according to any one of the preceding claims, wherein R_3 and/or R_4 are unsubstituted or are substituted by one or two substituents selected from aryl, heteroaryl and heterocyclic groups, alkyl, haloalkyl, halogen, nitro, -$S(O)_2$-alkyl, haloalkoxy, cyano, -CO_2R wherein R is aryl, heteroaryl, hydrogen or alkyl, alkoxy, hydroxy, -$CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, -Z-$NR'''R''''$ and -$NR'''R''''$ wherein Z is alkyl or alkenyl and R''' and R'''' are the same or different and each represent aryl, heteroaryl, hydrogen, alkyl or -CO-L wherein L is an alkyl or aryl group, and -O-Z-R''''' wherein Z is as defined above and R''''' is aryl, heteroaryl or heterocyclyl.

9. Use according to claim 1, wherein the bissulfonamide derivative of formula (I) is a bissulfonamide derivative of formula (Ia)



(Ia)

wherein R_5 to R_8 are as defined in claim 3, X and Y are the same or different and represent phenyl or thienyl, n represents an integer of from 0 to 4 when X is phenyl and an integer of from 0 to 3 when X is thienyl, m represents an integer of from 0 to 4 when Y is phenyl and an integer of from 0 to 3 when Y is thienyl, and R_3' and R_4' are the same or different and are selected from aryl, heteroaryl and heterocyclic groups, alkyl, haloalkyl, halogen, nitro, -$S(O)_2$-alkyl, alkoxy, haloalkoxy, cyano, -CO_2R wherein R is aryl, heteroaryl, hydrogen or alkyl, hydroxy, -$CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, -Z-$NR'''R''''$ and -$NR'''R''''$ wherein Z is alkyl or alkenyl and R''' and R'''' are the same or different and each represent aryl, heteroaryl, hydrogen, alkyl or -CO-L wherein L is an alkyl or aryl group and -O-Z-R''''' wherein Z is as defined above and R''''' is aryl, heteroaryl or heterocyclyl.

10. Use according to claim 9, wherein, in the formula (Ia), R_5 and R_8 are hydrogen, R_6 and R_7 are the same or different and are selected from aryl,

heteroaryl, nitro, cyano, alkyl, haloalkyl, halogen, hydrogen, -CO_2H, -CO_2-alkyl, alkoxy and -$CONR'R''$ wherein R' and R'' are the same or different and are aryl, heteroaryl, hydrogen or alkyl, or R_6 and R_7 together form an alkylenedioxy group or, together with the carbon atoms to which they are attached, form a further phenyl moiety, X and Y are the same or different and are phenyl or thienyl, n and m are the same or different and are 0, 1 or 2 and R_3' and R_4' are the same or different and are selected from:

(a) when attached to a phenyl moiety, aryl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, nitro, cyano, C_1-C_4 alkoxy, -CO_2R wherein R is hydrogen or C_1-C_4 alkyl, -$NR'R''$ wherein R' and R'' are the same or different and are hydrogen, C_1-C_4 alkyl or -CO-(C_1-C_4 alkyl), -O-(C_1-C_4 alkyl)-R'' wherein R'' is heteroaryl or heterocyclyl, and -$S(O)_2$-C_1-C_4 alkyl; and

(b) when attached to a thienyl moiety, pyridyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, nitro, halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, -CO_2R wherein R is hydrogen or C_1-C_4 alkyl, C_1-C_4 alkoxy, -(C_1-C_4 alkyl)-NH-aryl and -$S(O)_2$-C_1-C_4 alkyl.

11. Use according to any one of the preceding claims, wherein the medicament is for use in the inhibition of a dehydroquinate synthetase enzyme.

12. Use according to claim 11, wherein the dehydroquinate synthetase enzyme is AroB.

13. Use according to any one of the preceding claims, wherein the medicament is for use in the inhibition of a type II dehydroquinase enzyme.

14. Use according to claim 13, wherein the type II dehydroquinase enzyme is AroQ.

15. Use accordingly to any one of the preceding claims, wherein the medicament is for use in treating or preventing a bacterial or fungal infection.

16. Use according to claim 15 wherein the medicament is for use in the treatment or prevention of a Methicillin Resistant *Staphylococcus Aureus* infection.

17. Use accordingly to any one of claims 1 to 12, wherein the medicament is for use in the treatment or prevention of an infection by a parasite in which the biosynthesis of aromatic amino acids is effected via the shikimate pathway.

18. Use according to claim 17 wherein the medicament is for use in the treatment or prevention of malaria.

19. A herbicidal or fungicidal composition, comprising:
- a bissulfonamide derivative of formula (I), as defined in any one of claims 1 to 10, or an agriculturally acceptable salt thereof;
- at least one surfactant; and
- an agriculturally acceptable carrier or diluent;

20. Use of a bissulfonamide derivative of formula (I), as defined in any one of claims 1 to 10, or an agriculturally acceptable salt thereof, as a herbicide or a fungicide.

21. A method of controlling weeds or fungi at a locus, which method comprises administering thereto a bissulfonamide derivative of formula (I), as defined in any one of claims 1 to 10, or an agriculturally acceptable salt thereof, or a composition according to claim 19 or 32.

22. A method according to claim 21, wherein the locus comprises agricultural or horticultural plants or a medium in which such plants grow.

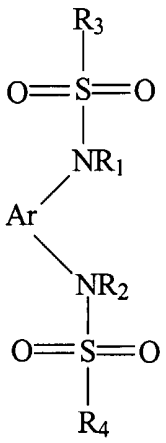
23. Use of a bissulfonamide derivative of formula (I) as defined in any one of claims 1 to 10, or a salt thereof, in controlling algae.

24. A method of treating algae in a fish tank or pond, which method comprises applying to the fish tank or pond a bissulfonamide derivative of formula (I), as defined in any one of claims 1 to 10, or a salt thereof.

25. Non-therapeutic use of a bissulfonamide derivative of formula (I), as defined in any one of claims 1 to 10, or a salt thereof, in inhibiting bacterial growth.

26. A surgical instrument having thereon an antibiotic coating comprising a bissulfonamide derivative of formula (I), as defined in any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.

27. A bissulfonamide derivative of formula (I), or a pharmaceutically acceptable salt thereof,

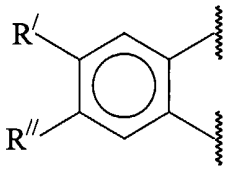


(I)

wherein:

- Ar is an aryl or heteroaryl group;
- R_1 and R_2 are the same or different and each represent hydrogen or alkyl or R_1 and R_2 together form a C_1-C_3 alkylene group, -CO- or -CS-; and
- R_3 and R_4 are the same or different and each represent an aryl or heteroaryl group,

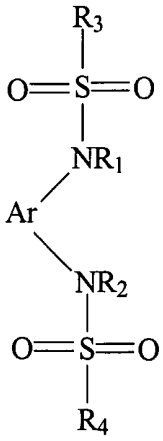
for use in a method of treating the human or animal body, provided that, when R_1 and R_2 are hydrogen and R_3 and R_4 are phenyl, 4-methylphenyl, or 4-aminophenyl Ar is not



wherein $R^{/}$ and $R^{//}$ are methyl or chlorine.

28. A pharmaceutical composition comprising a bissulfonamide derivative according to claim 27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

29. A bissulfonamide derivative of formula (Id), or a salt thereof,



(Id)

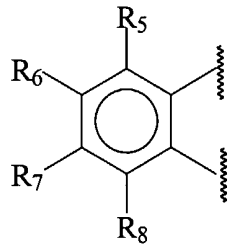
wherein:

- R_1 and R_2 are as defined in any one of claims 1 and 6;
- R_3 and R_4 are as defined in any one of claims 1, 7 and 8, and
- Ar is as defined in any one of claims 3 to 5

provided that when R_1 and R_2 are both hydrogen and Ar is an unsubstituted napthyl group, a phenanthracene group or a phenyl group optionally substituted by 1 or 2 dimethylmethylenedioxy, hydroxy, methoxy, ethoxy, methyl, chlorine, bromine, fluorine, nitro, CF_3 or amino groups, R_3 and R_4 are not (a) unsubstituted quinoline groups, (b) unsubstituted phenyl groups, (c) phenyl groups monosubstituted by a methyl, methoxy, $-CO_2H$, chlorine, cyano, nitro or amino group, or by a group $-O-CO-N(CH_3)-$ or (d) phenyl groups disubstituted by a nitro group and a methyl group.

30. A compound according to claim 29, wherein the bissulfonamide derivative of formula (1d) is a bissulfonamide derviate of formula (1a), as defined in claim 9 or 10.

31. A compound according to claim 30 wherein Ar represents a group



wherein R_5 to R_8 are as defined in any one of claims 3 to 5, provided that neither R_5 and R_6 nor R_7 and R_8 together form a phenyl moiety.

32. A compound according to claim 29, which is
1,2-Bis(4-trifluoromethyoxyphenylsulfonylamino)-4-chlorobenzene,
1,2-Bis(3-trifluoromethylphenylsulfonylamino)-4-chlorobenzene,
1,2-Bis(2,5-dichloro-3-thienylsulfonylamino)-4-chlorobenzene;
1,2-Bis(2-chloro-5-thienylsulfonylamino)-4-chlorobenzene;
1,2-Bis(2-methyl-3-chlorophenylsulfonylamino)-4-fluorobenzene;
1,2-Bis(2-chloro-5-thienylsulfonylamino)-4-fluorobenzene;

or a salt thereof.

33. A herbicidal or fungicidal composition comprising a bissulfonamide derivative of the formula (I), as defined in any one of claims 29 to 32, or an agriculturally acceptable salt thereof, and an agriculturally acceptable carrier or diluent.

34. Use of a bissulfonamide derivative of formula (I), as defined in any one of claims 1 to 10, or a salt thereof, in the inhibition of quinic acid catabolism.

35. Use according to claim 34, wherein the bissulfonamide or salt thereof is used to inhibit the catabolism of quinic acid by a fungus or a bacterium.